Pulmonary Carcinoma

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PATHOGENESIS, DIAGNOSIS, AND TREATMENT

Edited by

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and

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Foreword

Less than fifty years ago the author of a monograph on the subject of cancer of the lung could base his remarks on 312 authentic cases that had up to then been reported in the medical literature. Today—less than a lifetime later—312 cases of the same disease may be found in the course of a single year in a single city of the United States numbering two million souls. The recorded increase of bronchogenic cancer in the span of one generation has been called "the most violent phenomenon in the history of cancer." Competent authority has termed it "a pandemic disease in the United States and in the industrialized countries of Europe." The statement that no noninfectious disease has ever increased so rapidly is unchallenged. In the face of a health problem of such alarming proportions, a text summarizing the essential knowledge concerning the etiology, pathology, symptomatology, clinical course, diagnosis, management, and control of lung cancer should be welcomed by physicians and physicians-to-be. On them rests the responsibility of containing cancer of the lung as best as it may be contained, and at their hands—indeed in this book—are the facts which could make such containment possible.

On the other hand, the publication at this time of a text on pulmonary cancer is a brave venture, for the volume of data pertaining to this disease is in inverse proportion to the extent of professional agreement on many, including the most important, of its aspects. To begin with, there is a difference of opinion as to whether lung cancer is actually on the rise. The opponents of the evidence cite improved diagnosis and the aging population as adequate reasons for the apparent increase. Yet when adjustment is made for the factor of extended longevity, lung cancer is found to have increased by a degree far exceeding that recorded for any of the other varieties of cancer, in spite of the fact that the techniques for diagnosing it have not improved as much as have those for some other anatomical types. Moreover, age-standardized rates show an increase of death rate from cancer in general, exclusive of the lung, amounting to 2 per cent in the past twenty years, while during the same period, death rates from cancer of the lung have risen by over 250 per cent.

Perhaps no other disease can claim so many seriously proposed and well-supported etiologic vectors. Half a dozen occupational hazards, atmospheric pollutants, smoking and non-neoplastic chronic inflammatory

conditions have varying degrees and kinds of supporting evidence as inciters of cancer of the lung. But recognition of them is capricious and inconsistent. For example, industrial contact with certain chromium compounds is generally regarded as hazardous. The evidence is wholly epidemiologic: persons thus employed get lung cancer more frequently than those in other occupations. Although lung cancer has never been produced experimentally in any living organism by any chromium compound, the statistical evidence convinces everyone. On statistical grounds, the evidence incriminating cigarette smoking as being associated with lung cancer is even weightier than that for chromium. In addition there is laboratory evidence of a carcinogenic effect of condensed cigarette smoke—as measured by the mouse's skin. But, in this instance, the evidence is rejected by many—because "statistics don't prove anything," or because "a mouse is not a man," although it is widely conceded that the problems of experimental carcinogenesis are extremely complex; what will cause cancer in one organ of one species may not do so in the same organ of a different species, or in a different organ of the same species. All of which has led to the observation that if the degree of association now shown to exist between cigarette smoking and lung cancer were to be demonstrated for a relationship between crossing the Brooklyn Bridge and fatal accident, the bridge would be closed to traffic without demur.

There is a serious division of views concerning the value of early diagnosis. One school holds that lung cancers found in patients who have not yet developed symptoms are consistently resectable in a greater percentage of cases (and, by all that is reasonable, are more curable) than they are in patients who have begun to cough and wheeze, who have hemoptysis, or who suffer from the infectious sequels of lung tumor. The other view maintains that the histologic nature of the neoplasm is the only determinant of curability, regardless—or almost regardless—of when it is discovered.

A corollary of this argument is that concerning the usefulness of efforts to find lung cancer in presumably well persons: case-finding, or screening, by mass chest x-rays. Again the schism: on one side, those who say it is not worth the expense and the effort; on the other, those who, admitting its shortcomings, say it is the best weapon available, so why not use it? Perhaps the only points on which all are agreed is that cancer of the lung is undesirable and that surgery offers the only hope of cure.

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lem of truly alarming [illegible] tions in the [illegible]

polation of the present rate of rise indicates that lung cancer will soon become a major concern of every family doctor.

Second, it now appears likely that current investigations of certain alleged etiologic agents to which large numbers of the population are exposed, will establish their significance beyond cavil, and at that point the practitioner, in his traditional role as health counselor to his patients, may be provided with an instrument of preventive medicine of remarkable effectiveness. Even now, most of the physicians and scientists recently queried as to the advice they would give heavy cigarette smokers, are sufficiently impressed by the evidence to recommend reducing the amount of smoking or quitting altogether.

Third, assuming that lung cancer in the presymptomatic, or silent, phases is more curable than it is once symptoms have appeared—an assumption justified by data now coming to hand—the family doctor faces the duty of looking for it among his patients, including not only those who come to him for a "routine check-up," but, just as important, those who come to be treated for colds, backache, hernia, prostatism and what not. This concern to safeguard health by seeking out early disease is not accepted by all physicians. Yet in the light of the changing pattern of illness—primarily the dwindling importance of infections, and the emergence of the so-called degenerative diseases as the major medical problems of our time—the doctor can no longer serve his greatest usefulness by waiting for the bell to ring. If the problems of an aging population are to be met (and they will be met by the government if the profession will not meet them), the doctor is going to have to do some bell ringing himself, and it will not be embarrassing to do so, for public health propaganda from all corners, from official, voluntary, and professional organizations, are preparing the way.

Fourth, there can be no gainsaying the practitioner's responsibility to expedite the diagnosis of the patient with an abnormal chest roentgenogram or with complaints referable to the lung. Here, if anywhere, he should be at home—in differential diagnosis. Yet the fact, amply supported by the fate of those found to be "tumor suspects" following mass chest surveys, is that the family doctor to whom the problem is referred, often—too often—hesitates in pushing his patient through to definitive diagnosis. One of the more important missions of this volume is to make it clear that "good health" is consistent with x-ray evidence suggesting pulmonary cancer. Another aspect is presented by the patient with symptoms: the ubiquitous cough, chronic bronchitis, sinusitis, too much smoking, emphysema, atelectasis, virus pneumonia—how shall they be weighed? The lesson here is that no ready obvious explanation is justified until cancer of the lung is excluded. In view of the frequency of cancer,

not even the presence of tubercle bacilli may be accepted any longer as total evidence of a diagnosis.

Fifth, as the thresholds of operability are lowered, and as more operable patients are referred to surgeons, more postoperative problems are being returned to the family doctor. More and more, his is the task of supervising the patient's course following discharge from the hospital, with all the physical, psychic and social sequels involved; and they are all involved, regardless of what was accomplished in the operating room.

Finally, there usually falls to the family doctor the most exacting demand of all—that of accompanying to the end the patient who cannot be saved. Frustrating? By some standards, yes. Unrewarding? No. For just as obligating as the doctor's covenant to save life when he can, is his opportunity to help keep whatever of life remains bearable and acceptable—not only by mitigating bodily pain but, of greater concern to patient and family, by maintaining integration of personality, and when this becomes a losing battle, by making judicious concessions. Never do the ethics of medical practice permit the doctor to say to the patient, "There is nothing more I can do." He may, if in his judgment it is best, tell his patient he cannot get well, but not that he is without some resource. Most patients with hopeless cancer intuitively realize their plight. Usually they can adjust to the fatal prospect, but they cannot face abandonment The sensitive comments on the doctor's relations to the patient facing death, which are part of this text, can do much to sustain the patient (and the doctor as well), *in doing so, they go far in* abating the nuisance of quackery, for much of the quack's practice consists of abandoned patients

This compilation of authoritative statements on a health problem of growing oppressiveness comes none too soon As a summary of what is known that is of clinical usefulness, it deserves the attention of all doctors in general practice and those about to be.

CHARLES S CAMERON

Editors' Preface

A phenomenal increase in the incidence of pulmonary carcinoma has been reported from many parts of the world during the past few decades. Primary cancer of the lung, previously considered to be a relatively uncommon type of neoplasm, is now a topic of major clinical importance. The preparation of this volume was prompted by the belief that there was need for a presentation on cancer of the lung which encompassed all facets of pathogenesis, diagnosis, and therapy.

In view of the increasing incidence of certain types of lung cancer, a discussion of possible etiologic factors is presented by contributors actively engaged in such investigations. Also the various experimental approaches to lung cancer are described. The pathology of pulmonary neoplasms is presented from the standpoint of clinical correlation. The pathologic variations in lung cancer that emphasize the fallacy of considering all such neoplasms as a single disease entity are indicated.

This volume presents a discussion of the many aspects of cancers of the lung that play a role in diagnosis and therapy. Pitfalls in the early recognition of pulmonary carcinoma are emphasized by the inclusion of a section with short case reports illustrating many of the common problems in differential diagnosis and management. The relative values of the various diagnostic procedures are thoroughly analyzed by contributors who have had wide clinical experience in dealing with pulmonary neoplasms.

The role of surgical therapy in pulmonary carcinoma is presented and analyzed with a detailed consideration of factors influencing the surgical indications and results. Those aspects of pulmonary function that are important in the clinical evaluation of the patient undergoing surgical treatment are assessed. Chapters on radiation therapy, chemotherapy, the use of isotopes, and the medical management of inoperable cases will give the clinician a complete survey of the over-all therapeutic armamentarium in combating pulmonary cancers, both primary and metastatic. Finally the psychologic aspects, which can be an important problem for the medical practitioner in such a chronic illness, are presented.

Our objective has been to produce a predominantly practical book written by clinicians and specialists reflecting for the most part their own views and opinions gleaned from an extensive clinical experience. Our

goal was a book that will commend itself to the practitioner of medicine who is in need of guidance in his constant fight against this increasingly prevalent disease.

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Contents

Pulmonary Carcinoma

1

Modern Concepts of Cancer Research

CORNELIUS P. RHOADS

The search for control and the eventual prevention of the neoplastic process has undergone an interesting series of developmental steps. It began with the consideration of cancer as the expression of some omnipotent force of supernatural origin, moved into the descriptive phase with the development of pathologic anatomy, and then shifted in an effort to fall in line with the newly discovered bacterial etiology of disease. Later, it moved back into the mysterious force stage, with cancer regarded as a distorted expression of the growth process. Now the thinking has come all the way back to the early consideration of the neoplastic cell as an infecting microorganism, with its origin in a somatic mutation or a permanently acquired characteristic, and with cure to be sought by its control or destruction. Indeed, modern thought has now crystallized in a concept of cancer as a useful expression of Darwinism—the survival of the fittest mutation—reduced to a cytologic basis. Under this concept the competence of the organism and the environment in which it finds itself achieve expression in the invasive or non-invasive growth of the mutant form.

The earlier considerations of cancer, from Hippocrates through Galen to Paracelsus, solely concerned the possibility of a humoral origin. It is entertaining to observe that the claim of Galen that cancer was due to a concentration of black bile, may in the near future be expressed by the definition in bile of constituents so modified as to be cancer-producing. In the same way, the ancient feeling that cancer was due to mineral salts in the blood may turn out to have some factual basis in our knowledge of trace metals as required for a variety of kinetic reactions.

Further advances came with recognition of the local origin of cancer, with the concept of a specific virus presumed to make normal cells neoplastic, and with the idea of cachexia as a systemic manifestation of the neoplastic process—observations as pertinent today as they were in 1735.

Even the notion of John Hunter that cancer was due to coagulated lymph is borne out to some extent by Stewart and Treves' recent description of sarcoma developing in the lymphedematous arm following radical mastectomy Truly there is nothing new.

The classic study of Johannes Muller firmly established the cytologic basis of cancer—and something more, its origin in abnormal cells, regarded as germ cells, scattered among the normal tissue elements. Recognition of cancer as an abnormal cellular growth was amplified and extended by the classic work of Virchow. By an interesting coincidence, this came with the recognition of other cells, bacteria described by Pasteur in 1864 as causing spoilage of wine and later proved to cause disease in man. The impact of this discovery can scarcely be estimated in modern times It was the first real knowledge of the cause of formerly mysterious biological events, called disease, and as such it threw into obscurity every disease process but those of an infectious nature Hence it is wholly understandable that such cancer research as was done attempted to define, in the growth, some kind of infecting microorganism capable of giving rise to the characteristic aggregation of cytologic units which compose the neoplasm

It is interesting that Ehrlich was the one person of these early days who recognized the cancer cell as the infecting microorganism itself, arising from normal cells by some sort of irreversible change He therefore began his work on cancer about 1900, in the belief that the cytologic theory of specific chemical fixation to specific cell constituents, which he had applied to the destruction of parasitic invading microorganisms derived from the outside environment, might apply as well to the control or destruction of the cancer cell

It is astonishing to recognize, fifty years later, in the athreptic theory of immunity defined by Ehrlich, the belief that the immune body choked off the nutrition of the antigenic cell—the antimetabolite principle presently applicable to the control of transplantable tumors in experimental animals

Ehrlich made even more basic observations pertinent to the cancer problem Impressed with the early experiments on tumor transplantation, he undertook a series of experiments that duplicate those of a number of present-day laboratories. The increase of growth capacity on persistent transplantation, the immunization with attenuated tumor, the morphologic change with continued passages, and the effect of the transplantation on the tissues of the host, are still the subjects of investigation It is only unfortunate that the emphasis on the chemotherapy of infectious diseases diverted Ehrlich's attention from his manifest plans to seek chemical control of cancer.

In 1911 came the next step, the publication by Rous of the fact that

cell-free filtrates of a spontaneous malignant neoplasm of fowls would induce similar growths in normal birds. This observation was rapidly confirmed and extended to other fowl tumors It led, furthermore, to a long series of studies in a number of laboratories that have established unequivocally the role of cell constituents in cancer induction It is apparent from these studies that certain neoplasms can be induced by the inoculation of cytologic fragments of less than cellular size derived from spontaneous tumors, sometimes by their inheritance, and occasionally—as in the case of fowl leucosis and the Shope papilloma—by contagion

Noteworthy as these experiments are, and compatible as they are with the infectious nature of disease, the fact should not be forgotten that the vast majority of neoplasms has not been demonstrated to be transmissible by filtrates, particularly in mammals Furthermore, characteristic new growths can be induced by a variety of physical and chemical means, clearly capable of causing changes (mutations) in somatic cells which can be propagated indefinitely by transplanting intact cytologic units, but not any cell-free materials

The effort to force the cancer problem into the framework of infectious disease by defining an infectious cause of the cancer cell, effectively blocked another concept of the neoplastic process. This concept is one which would justify a search for cancer control by those methods which have been so effective in the control of infecting microorganisms. The dream that a virus could be found which then could be cultivated, attenuated, and employed as an immunizing vaccine to induce a permanent immunity to all forms of cancer, was an attractive one indeed However, it was highly incompatible with the experimental observations In light of the present knowledge, it would be manifestly extraordinary to find a single virus that caused such a wide variety of anatomical changes Every effort to immunize by whole or extracted in-strain tumors against spontaneous disease has failed. The most assiduous and protracted efforts to demonstrate active filtrates for human cancer have been fruitless. This does not in any sense deny that the neoplastic process may be transferred from cell to cell by minute cytologic units. It simply indicates the conviction that concentration on this channel for cancer control, in the hands of the most experienced and determined investigators, has regularly encountered such apparently insurmountable walls that a new approach is justified

The repeated and tantalizing failure to demonstrate an etiologic microorganism as the cause of cancer was in sharp contrast to the regular, irrefutable ability to produce cancer cells from normal ones by employing nonliving agents This led to the concept of cancer as a perversion of th growth process, and the search for its control in those factors which lim

that function. Furthermore, as with the virus theory, there was just enough foundation for this concept to justify the effort. There is strong evidence at hand that many types of cancer are not entirely autonomous, at least for a considerable period. Rather, for a time they are distinctly dependent on those factors of a hormonal nature which favor or suppress the growth of their normal prototypes. Studies from many laboratories on cancer of the breast, prostate, and thyroid of man amply establish this fact Nevertheless the fact remains that in the 58 years during which cancer cure has been sought in the factors controlling normal growth, not a single patient or animal with cancer has been cured by those means.

Indeed, an extremely interesting dichotomy of thinking has developed among those interested in cancer control and committed to its improvement. Today, as a century ago, the only means for the cure of cancer is in the mechanical (surgical or radiologic) elimination of a localized nidus of cancer cells As a consequence, much of the thinking and planning for control of disseminated cancer (which accounts for 75 per cent of all the patients) has been done by masters of mechanical extirpation or of morphology This is the case despite the fairly obvious fact that, due to that very mastery, the competence to seek—and find—nonmechanical means is effectively eliminated. Hence, the derision offered those individuals so misguided as to seek control of disseminated cancer by the chemical principles that have brought the death rate from infectious disease to the vanishing point

In contrast to the masters of mechanical cancer cure is the great school which holds that better control of cancer can only come by broadening the activity in the departments of natural sciences The justification for this belief is found in the conviction that cancer is some kind of a riddle, or mystery, which must be entirely unraveled before any hope for better cure or prevention can be entertained According to this principle, there is financed, under the term of cancer research, practically every type of activity in the natural sciences Heavy support goes into physics, since physical tools—x-rays and radium—have a demonstrable usefulness in curing a limited number of forms of localized cancer, and in restraining certain forms of advanced disease. Prodigious aid is given to basic biology, particularly animal genetics, in the expectation that data derived from pure lines of animals will be applicable to impure lines of human beings. Growth in almost every aspect—and there are many—is investigated intensively, from viruses to bacteria, through earthworms to the horns of sheep and deer Not only are the forms and details of growth scrutinized with every penetrating tool of modern science, but its functions in physical and chemical terms are also examined. Just about every aspect of biochemistry and endocrinology is under the most

intense study, with particular reference to those areas which are concerned with the growth and reproduction of living systems. And this is all good, since knowledge is being amassed to an extent and degree that would be quite impossible were it not for the public determination to leave unturned no stone that could conceal a method for cancer control

It is important, however, to be certain that in this flood of new information, the conceptual key to cancer control is not obscured or lost sight of altogether And careful scrutiny suggests that such a disastrous contingency is not entirely impossible.

Those working for cancer control fall into two groups The first includes the mechanical and morphologic masters of cancer control as it exists today Their techniques apply only to localized disease, and this accounts for only 25 per cent of all the cancer patients now coming under care or likely to do so in the foreseeable future.

The second group includes those masters of the natural sciences who draw support from cancer funds and study various aspects of growth as a whole with the greatest skill, but study them entirely as techniques that are ends in themselves These highly qualified scientists work as biologists, or biochemists, or organic chemists, or physicists, attracting and educating graduate students, and making fine, precise, and basic scientific contributions They are technical experts in methodology, implicit to cancer control These techniques are well-established and satisfactory lifetime pursuits as ends in themselves The great problem, however, is how to use them to make an end to cancer

There are, then, those who know cancer in man as it exists, and make its limited control possible There are, on the other hand, those who study disciplines in which specific directions are needed to make an end to cancer Between the two groups there yawns a great chasm of mutual misunderstanding. If it is not bridged, and soon, those responsible for cancer progress, and expending prodigious funds to attain it, will be remiss to themselves, to the public, and to posterity

However, it is possible to draw from the present information a perfectly rational concept for the advance toward cancer control. Not only is such a concept feasible and documentable, but limited experimentation based upon it has already yielded important advances

The first step in the modern concept is the decision to approach the solution of the cancer problem directly, to seek the cure of cancer in man, and eventually to define its cause and to eliminate it completely This is a particularly difficult step, since it denies the vast weight of precedent embodied in the "mystery concept" of the disease, the belief that nothing in the future can be done better than it is being done today. Remarkably enough, a substantial weight of opinion inclines toward this

point of view, despite every evidence that it has never, in all history, been correct.

To approach our first goal, *the cure of disseminated cancer, the second* step is to gain some evidence that cancer is a curable disease This is at hand in the fact that cancer is curable today, and has been for more than fifty years, if it is entirely removed by mechanical means. Clearly, then, rather than pursuing some devious consideration of a mystery, it would be well to consider how to remove every cell of disseminated cancer by other means, since the mechanical approach is obviously excluded.

The third step is to define some principle which will permit the selective removal of one group of widely disseminated cells, in this case cancer, without the concurrent removal of any other cell type essential for life. Of course, this principle has already been at hand since 1911 when salvarsan proved itself It has been so amply confirmed for so many types of infectious invaders that disease due to them has virtually disappeared.

The fourth step is the recognition of the principle of selective cell destruction as it applies to cancer cells. This step is a difficult one. It is easy to recognize a bacterium, a malarial parasite, or a trypanosome as a foreign invader whose destruction must be sought if cure is to be achieved For some reason it is very difficult for the investigator to regard the cancer cell in this light. This difficulty is hard to understand today, since now we can make the cancer cells of man do essentially every stunt possible to bacteria. We can observe them in the lesion regularly We can cultivate them in profusion in glass, in the embryonated fowl egg, and in the experimental animal. They grow as well as in the original hosts—indeed, in many instances better. They retain not only their original morphologic characteristics, but also their human chromosomes and protein components They can be transplanted back into their original hosts with exact duplication of the original cytologic characteristics. And finally, in the human body they appear to acquire resistance to, and even dependence on, chemicals which injure or even destroy their progenitors and siblings. If there is any competence possible to the bacterium that cannot be duplicated today by cultured human cancer cells, it is not one known to this writer.

There seems then to be no reason why the bacterium, by conventional and accepted criteria, should not be regarded as analogous to the cancer cell Nevertheless, the skeptic will continue to advance the classic argument in opposition, that the bacterium comes from the external environment while the cancer cell is found in the normal units of the human structure itself, and so must be insusceptible to selective destruction Even this argument can now be countered. The demonstration that phage can be made manifest in bacteria otherwise seemingly devoid of these units, that viruses are carried for years if not for generations in

hidden and silent form, that avirulent normal benign bacterial inhabitants of the nasopharynx can be converted to virulent invaders, all indicate the amazing mutability of biological units The acquisition of resistance by bacteria renders such forms as malignant in relation to their nonresistant relatives in a suitable environment as cancer cells are in comparison to normal cells of the mammal. Every bit of evidence from modern microbiology indicates that a single genetic change in a strain of bacteria, derived from a single original cell, can induce a new strain as different from the original in susceptibility to destruction, as any bacterium susceptible to penicillin differs from the cells of the host which it invades. And no evidence exists that the cancer cell is any less sensitive to selective injury than its bacterial analogue.

The next, and fifth, step, however, is to prove that the theoretical consideration is correct, that the cancer cell can be destroyed by chemicals which are innocuous to normal cells growing at the same rate This has now been done Biesele (1) has grown normal and neoplastic cells of similar origin from experimental animals, at the same rate, as judged by mitotic counts, and side by side in the same roller tube culture. The addition to the culture of certain modified precursors of nucleic acid has resulted in destruction of the neoplastic units by concentrations which are without effect on their normal relatives Furthermore, this is not confined to in vitro experiments Stock and his co-workers (2) have shown conclusively that certain transplantable neoplasms of mice and rats can be regularly and completely destroyed by chemicals, alone or in combination, which exert little or no effect upon the host

In short, the cure of transplantable cancer in experimental animals by chemicals *is a fact today*, not a nebulous chimera to be sought only by the eccentric and the quack

The sixth step is perhaps more important It is the discovery of some rational procedure by which the more selective destruction of cancer as compared to normal cells can be approached by chemical means. Such a rationale is now at hand It is called the "heterogeneity of nucleic acid metabolism" This simply means that the hereditary material of the cell, the nucleic acid, is in dynamic equilibrium, that preformed, complex precursors as well as simple molecules are employed in this dynamic process, and, most important, that the composition, and so the dynamic requirements of each type of cell, differs from any other This has now been amply established by Bendich, Russell, and Brown (3) It is confirmed by the observations of Chargaff (4), G L Brown and Watson (5), Cavalieri (6), and G B. Brown (7), all indicating the heterogeneity of *composition* as well as of metabolism of nucleic acid

The next point, the seventh in the sequence, is to prove that this specific heterogeneity can serve as a basis for the use of the antimetabolite prin-

point of view, despite every evidence that it has never, in all history, been correct.

[illegible] econd [illegible] s is at [illegible] than fifty years, if it is entirely removed by mechanical means. Clearly, then, rather than pursuing some devious consideration of a mystery, it would be well to consider how to remove every cell of disseminated cancer by other means, since the mechanical approach is obviously excluded.

The third step is to define some principle which will permit the selective removal of one group of widely disseminated cells, in this case cancer, without the concurrent removal of any other cell type essential for life. Of course, this principle has already been at hand since 1911 when salvarsan proved itself. It has been so amply confirmed for so many types of infectious invaders that disease due to them has virtually disappeared.

The fourth step is the recognition of the principle of selective cell destruction as it applies to cancer cells. This step is a difficult one. It is easy to recognize a bacterium, a malarial parasite, or a trypanosome as a foreign invader whose destruction must be sought if cure is to be achieved. For some *reason* it is very difficult for the investigator to regard the cancer cell *in this light. This difficulty is hard to understand* today, since now we can make the cancer cells of man do essentially every stunt possible to bacteria. We can observe them in the lesion regularly. We can cultivate them in profusion in glass, in the embryonated fowl egg, and in the experimental animal. They grow as well as in the original hosts—indeed, in many instances better. They *retain* not only their original morphologic characteristics, but also their human chromosomes and protein components. They can be transplanted back into their original hosts with exact duplication of the original cytologic characteristics. And finally, in the human body they appear to acquire resistance to, and even dependence on, chemicals which injure or even destroy their progenitors and siblings. If there is any competence possible to the bacterium that cannot be duplicated today by cultured human cancer cells, it is not one known to this writer.

There seems then to be no reason why the bacterium, by conventional and accepted criteria, should not be regarded as analogous to the cancer cell. Nevertheless, the skeptic will continue to advance the classic argument in opposition, that the bacterium comes from the external environment while the cancer cell is found in the normal units of the human structure itself, and so must be insusceptible to selective destruction. Even this argument can now be countered. The demonstration that phage can be made manifest in bacteria otherwise seemingly devoid of these units, that viruses are carried for years if not for generations in

hidden and silent form, that avirulent normal benign bacterial inhabitants of the nasopharynx can be converted to virulent invaders, all indicate the amazing mutability of biological units The acquisition of resistance by bacteria renders such forms as malignant in relation to their nonresistant relatives in a suitable environment as cancer cells are in comparison to normal cells of the mammal. Every bit of evidence from modern microbiology indicates that a single genetic change in a strain of bacteria, derived from a single original cell, can induce a new strain as different from the original in susceptibility to destruction, as any bacterium susceptible to penicillin differs from the cells of the host which it invades. And no evidence exists that the cancer cell is any less sensitive to selective injury than its bacterial analogue.

The next, and fifth, step, however, is to prove that the theoretical consideration is correct, that the cancer cell can be destroyed by chemicals which are innocuous to normal cells growing at the same rate. This has now been done Biesele (1) has grown normal and neoplastic cells of similar origin from experimental animals, at the same rate, as judged by mitotic counts, and side by side in the same roller tube culture. The addition to the culture of certain modified precursors of nucleic acid has resulted in destruction of the neoplastic units by concentrations which are without effect on their normal relatives. Furthermore, this is not confined to in vitro experiments Stock and his co-workers (2) have shown conclusively that certain transplantable neoplasms of mice and rats can be regularly and completely destroyed by chemicals, alone or in combination, which exert little or no effect upon the host.

In short, the cure of transplantable cancer in experimental animals by chemicals *is a fact today*, not a nebulous chimera to be sought only by the eccentric and the quack

The sixth step is perhaps more important. It is the discovery of some rational procedure by which the more selective destruction of cancer as compared to normal cells can be approached by chemical means Such a rationale is now at hand It is called the "heterogeneity of nucleic acid metabolism" This simply means that the hereditary material of the cell, the nucleic acid, is in dynamic equilibrium, that preformed, complex precursors as well as simple molecules are employed in this dynamic process, and, most important, that the composition, and so the dynamic requirements of each type of cell, differs from any other. This has now been amply established by Bendich, Russell, and Brown (3). It is confirmed by the observations of Chargaff (4), G L. Brown and Watson (5), Cavalieri (6), and G B Brown (7), all indicating the heterogeneity of *composition* as well as of metabolism of nucleic acid.

The next point, the seventh in the sequence, is to prove that this specific heterogeneity can serve as a basis for the use of the antimetabolite prin-

ciple so long recognized in pharmacology and bacteriology and so little *acknowledged as applicable to cancer control.* Here once again the observations of Stock and his associates (2) are outstanding. Biesele (1) has shown in vitro the astonishing specificity of action of modified nucleic acid precursors on normal and neoplastic units, Hitchings (8) has made similar demonstrations for closely related bacterial strains, Philips (9) has shown an astonishing specificity for different normal tissues, as have Stock, Clarke, and Sugiura (2) for a variety of transplantable animal tumors.

Finally, perhaps the most conclusive and exciting development is that of Skipper (10) and Balis (11), who by preliminary and incomplete data have indicated that human cancer implants—like those of animals—have *uptake patterns different from normal tissues for nucleic acid precursors.* Furthermore, they have perhaps a different susceptibility to injury by modifications of those precursors

The evidence presented, in support of a firm program for cancer chemotherapy, is sound and adequate but not final. *The only final proof* is the accomplishment of cancer control in man based upon the principles so clearly established for experimental animals. This is not at hand and the reason for its lack is apparent Until now there has been only animal cancer available for test on a reproducible basis The whole rational thesis of chemotherapy described depends upon specific uptake patterns by specific cells, by species, by types, and by degrees of maturity. Obviously, then, with only mouse cancer to test, fine cures for mouse cancer have been discovered. Just as obviously, these are not applicable to the human disease to any substantial degree, nor should they be if our thesis is correct That they are, to a minute degree, so applicable, is clearly *good fortune and not good planning.*

What the future will hold concerning this thesis only the future can tell All that can be said at the moment is that few pictures of disease control have looked so nearly complete, or so promising, before the fact *It would be distressing and disappointing indeed if this promise is not* borne out in time.

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2

The Biology of Cancer with Special Reference to Cancer of the Lung. Experimental Studies

WILLIAM E. SMITH

Cords of cells growing into the skin in multiple directions from a central mass in the breast suggested the outline of a crab to the eyes of ancient Greek physicians. They used their word for crab to describe this lesion, and their word, "cancer," has since been applied to invasive growths in other areas of the body. Such growths of bone have been found in Egyptian mummies. For centuries, comprehension of the normal anatomy of the human body was confused by the description of structures interpreted as internal organs and found in some individuals but not in others Many of these structures were undoubtedly cancers. In thinking about the diseases we describe as cancer, we are therefore concerned with a type of atypical growth that has afflicted the human race for a long time.

The study of primary cancer of the lungs has been traced back to the sixteenth century, when a curious lung disease was described among men who worked in certain German mines now known to contain radioactive ores (1). Over the years, this disease continued to afflict miners employed there. In 1879 it was recognized as cancer In the eighteenth century, lung cancer was diagnosed at an autopsy in Italy by Morgagni, and in France this disease was described by Laennec. William Stokes published his studies of lung cancer in Dublin in 1837. Some interesting comments upon these and other early accounts of cancer in this site have been published (2, 3) But man does not suffer alone Primary pulmonary neoplasms have been described in the cat, civet, cow, dog, fowl, guinea pig, horse, kangaroo, jaguar, mouse, opossum and sheep (4-7).

It is noteworthy that cancer is not a peculiarly human affliction. Tumors of one sort or another occur in many species of mammals (6, 7), in birds (8, 9), in amphibia and fish (10), and even in invertebrates (11).

Some pathologic growths of plants may be regarded as tumors (10) The intensive studies of human pathology made with the microscope during the past century have revealed that tumors can arise from the majority of cell types present in the human body. Tumors arising from cells of many different tissues have also been found in mice (12) By comparison with the data available from men and mice, less information exists about the variety and frequency of tumors in other species It can be argued that species other than man and mouse have been less intensively studied for this purpose, and that wild animals or animals raised in great number for food are less likely to survive to the advanced ages when cancer is most common Both these arguments have merit, but they should not lead us to assume that intensive studies of other species will eventually disclose the array of tumors found in man, or even in mice, nor to assume that malignant growth is a fate that may overtake any cell of any species Indeed, differences in the types of tumors or in the frequency of tumors in different species may provide clues for the development of fundamental concepts

One of the fundamental findings that have been derived from experiments upon tumors in animals was the discovery by Peyton Rous (8) in 1911 that cell-free extracts of a chicken sarcoma could, on injection into healthy chickens, bring about the development of similar tumors in them Various types of tumors in a number of different species, including some warts in man, have subsequently been demonstrated as transmissible in this way, and the agents responsible for the effects are spoken of as tumor viruses (10) These viruses are notably restricted in their tumorigenic action to certain tissues Some act upon mesenchymal cells and elicit sarcomas, others upon epithelial cells with resultant warts and carcinomas, some affect blood cells and induce leukemias The need for a particular cell-substrate is well illustrated by experiments with a virus that induces papillomas when inoculated into the skin of rabbits. When the site of inoculation is moved a few millimeters away from the skin epithelium and the virus is introduced into the mucosal epithelium of the lip, it has no tumorigenic action whatsoever (13) Another virus, which produces tumors of the mucosal epithelium, fails to do so upon the skin (14) An agent such as that which induces mammary cancer in mice thus poses no threat to fish, which possess no mammary tissue for it to act upon Less facetiously, the tumor viruses are notably limited as to the species in which they can act The virus that elicits skin tumors in rabbits has no effect upon mice, and the viruses that induce leukemias or sarcomas in fowls fail to do so in mammals The existence of a virus capable of inducing tumors in one species, and the absence of such a virus in another, could well determine differences in the tumor experience of the two species

As in the viruses, there is also variation in the susceptibility of tissues to the tumorigenic action of certain chemicals. No skin tumors are elicited by betanaphthylamine, paradimethylamino-azobenzene, or acetylaminofluorene, compounds which evoke tumors in internal organs. A chemical that produces tumors in one species may fail to do so in another. Benzpyrene or methylcholanthrene, which readily induce cancer when painted upon the skin of mice, seldom do so when applied to rats, although both species respond readily with sarcomas when either of these chemicals are introduced subcutaneously (15). Methylcholanthrene, one of the most potent carcinogens known, as judged by tests upon mice, failed to induce any tumors when applied repeatedly to monkeys over a period of twelve years (16) Cancer has been produced in monkeys painted for six years with a petroleum derivative that also caused tumors when applied to the skin of mice and rabbits, but concurrent tests of this same oil upon rats and guinea pigs were completely negative (17). The dye, paradimethylamino-azobenzene, which readily causes liver tumors when fed to rats, seldom does so in mice and never in chickens. In seeking explanations for differences in the reactions of different species, E C and J A Miller and their associates noticed that this dye combined firmly with liver proteins of rats, and less firmly with those from mice. There was no binding of the dye by liver proteins from chickens, cotton rats, guinea pigs, or rabbits, species which are highly resistant to the carcinogenic action of this compound (18).

Some exceedingly thought-provoking experience has emerged from the study of betanaphthylamine, a substance used in the manufacture of certain dyes. Cancer of the bladder has been recognized as an occupational hazard for men working with this chemical, but tests of it in a variety of species of animals failed for years to indicate any carcinogenic properties Eventually, dogs were utilized as a test species, and tumors resulted in their bladders when the compound was fed to them (19) Studies of the metabolic fate of this compound were subsequently undertaken, and hydroxylated derivatives were identified in the urine. The pattern of hydroxylation was found to differ in different species. Georgianna Bonser and her co-workers showed that one of these derivatives, 2-amino-1-naphthol, found in the urine of man and the dog, was less readily produced in the cat, mouse, rat, and rabbit This particular metabolic derivative was then shown to be capable of causing cancer of the bladder in mice, a species that does not develop cancer in response to betanaphthylamine itself These experiments indicate a fundamental concept of major significance, namely, that a compound that may possess no primary carcinogenicity can acquire such a property through metabolic changes impressed upon it in the bodies of animals of some species but not in others (20, 21, 22). It may be that such differences between

individuals within the same species determine why one will form a tumor while another will not, after both are exposed to the same agent.

Much has been attempted to explore the mechanisms whereby chemical carcinogens exert their effects upon cells The findings and speculations in this area have been shrewdly and succinctly reviewed by Boyland (23). Whatever these mechanisms may be, it is noteworthy that they can sometimes be modified The carcinogenic action of certain chemicals can be inhibited by simultaneous exposure to closely related but non-carcinogenic compounds (24, 25). Conversely, a few applications of a carcinogen to the skin, insufficient to elicit cancer there, may do so when the treated skin is subsequently subjected to a mechanical injury or to an irritant (26). Such an injury or irritant is spoken of as a promoting or co-carcinogenic stimulus. This phenomenon might well play a role in determining why, in groups exposed to the same carcinogen, some individuals develop cancer while others do not It is not known whether co-carcinogenic influences play a role in cancer of the respiratory system, but the diverse industrial dusts associated with cancer of the respiratory system in certain occupational groups (27) and in some experimental studies (28) suggest that research into this field may prove rewarding It is known that the lungs of different species respond differently to the same irritant Asbestos produces a pneumoconiosis in rats, rabbits, and guinea pigs resembling that which it causes in man, but it fails to do so in mice or dogs (29).

Investigation of genetic factors in cancer has provided a great field of fundamental inquiry There is a long list of benign and malignant tumors of human beings in which heredity is thought to play some role (30) Lung cancer has not yet appeared on this list, perhaps because until present generations it has been so seldom recognized that detection of several cases in one family has been unlikely With the numbers of lung cancers diagnosed in generations now living, it should be possible to learn whether there is any familial tendency to this disease

A wealth of knowledge has been gleaned from genetic experiments with animals (31) These experiments have been accomplished by mating the progeny of a parent who bore the type of tumor desired for the study Similar brother-sister matings of subsequent generations were then carried out, with discarding of descendants of parents in whom the desired neoplasms did not appear After many generations of such selective breeding, strains of mice have been developed in which almost all members surviving into the older age groups develop mammary cancer, whereas in other strains almost all members develop leukemia, and in still others almost all develop pulmonary tumors It has also proved possible to develop strains having a low or moderate incidence of these or other tumors

In 1933, evidence began to appear showing that the tendency to mammary cancer was transmitted by the female parent but not by the male (32). Sucklings born of mothers from a strain free of mammary cancer developed this disease in old age if nursed when young by mothers from a strain having a high frequency of mammary cancer. The reverse experiment also succeeded. Mammary cancer did not appear in the progeny of mothers of high mammary cancer strains if the babies were removed from their mothers before taking any milk, and were then foster-nursed by mothers free from breast cancer.

The discovery of the transmission of the liability to this form of cancer by an agent, presumably a virus, in the milk, opened avenues of thought of profound importance. Not only did it afford an explanation for the appearance of cancer in families previously free of it, but search techniques for viral agents of cancer were immensely broadened. The previously known viral agents of chicken sarcomas and leukemias and of rabbit papillomas asserted their presence, like other viruses, by inducing their characteristic lesions within a few weeks. But the mammary tumor agent, acquired during the first days of life, remained unsuspected in the tissues until late in the life of the animals. Further, the activity of this agent is conditioned by the genetic constitution of the hosts and by hormonal stimulation. Pregnancy or injections of estrogens speed the rate of appearance of breast cancer in individuals harboring the agent, and increase the eventual frequency of the tumors (33).

Recently, it has been claimed that leukemia in mice is caused by a virus transmitted from one generation to another through the embryos, and that leukemia can be made to appear in families of mice previously free of that disease by injection of extracts of leukemic tissues into newborn animals (10), but these experiments have failed of confirmation (34). No evidence has yet appeared to indicate that the pulmonary adenomas, common in certain mouse strains but not in others, have a viral etiology. Unpublished experiments conducted by Peyton Rous and this writer yielded no increased frequency of these tumors in mice observed throughout their lives after intranasal insufflation or intrapulmonary injection of cell-free extracts of adenomas into newborn animals.

Claims have been made, however, for the demonstration of a virus in pulmonary adenomatosis of sheep. This disease (jaagsiekte) has assumed epidemic proportions in sheep in some parts of the world. It apparently does not spread to the shepherds of diseased flocks, but occasional cases simulating this disease are found in man. It is a more diffuse process than the pulmonary adenomas of mice, but the cells have a similar appearance. Niels Dungal (35), in Iceland, has reported the following results in experiments with it. The disease was seen to develop in healthy sheep housed above sick sheep. A diseased sheep was made

to breathe through a 20 per cent glycerin-saline solution and this solution was introduced intratracheally into each of three lambs, in two of which the disease developed. The breath of one of these, collected in glycerin-saline, was filtered through collodion membranes and the filtrate was injected into the lungs of four mice. These mice were killed four months later, and one had what was considered *jaagsiekte*. These experiments suggest that a virus is responsible for pulmonary adenomatosis in sheep, but the finding of adenomatosis in only two lambs, on an island where the disease is endemic, and in only one mouse, precludes a conclusion at present. In sheep, the disease is often complicated by pneumonia, but the pulmonary adenomas of mice occur free of inflammatory changes (36).

In discussing the various types of tumors that have been transmitted to new hosts by cell-free extracts of tumor tissue, the phrase "tumor viruses" has thus far been used in this chapter. This is the phrase generally

lifeless media, and increase in number of pathogenic particles upon introduction into living cells (37). Nevertheless, one may question whether the particles capable of transmitting tumors are fundamentally akin to agents such as the influenza or vaccinia viruses. The problem concerns the evolutionary origin of viruses. If pathogenic self-duplicating particles such as the influenza or vaccinia virus arose through development of a state of obligate intracellular parasitism by microorganisms, then these viruses can be said to have an exogenous origin in respect to higher forms of life. The tumor viruses, on the other hand, might conceivably owe their origin to pathologic changes in components of the cells of the species in which they exert their effects. This question, considered upon the discovery of the first tumor virus (8) but still unsolved, gains stature by reference to the self-propagating particles known as plasmagenes in plants and protozoa. Plasmagenes are transmitted by heredity but lie outside the nucleus. They determine some cellular characteristics and may, on occasion, give rise to abnormalities. An analogy between plasmagenes and tumor viruses leads to intriguing speculations (38). Recently, it has been claimed that lymphosarcomas and chemically induced hepatomas of rats can be transmitted by their mitochondria (39), but in these experiments the possibility of the presence of intact cells, and hence of simple tumor transplantation, could not be excluded. The same reservation may apply to the claim that sarcomas induced in mice by dibenzanthracene can be transmitted to new hosts by extracts of the tumors (40).

Following the influenza epidemic of 1918, many pathologists described metaplastic changes in the bronchial epithelium of persons dying as a result of that disease, and views were advanced that these changes were precancerous and indeed that some cases of lung cancer could be regarded as sequels of influenza The literature of that period has been reviewed by Simons (41), who pointed out that if influenza can lead to lung cancer, it cannot be the only cause, since many cases of lung cancer occur without a preceding history of influenza. In the extensive study of the pathology of influenza published in 1920 by Winternitz, Wason, and McNamara (42), the statement is made

> In a number of cases, epithelial proliferation has been so extensive that it could not be differentiated histologically from an invasive malignant neoplasm There is no reason to believe that malignancy might not result from the continuous stimulation of the epithelium to proliferate in the chronic inflammatory process of the lung in influenza just as chronic infection in the lung of a mouse results in a much higher percentage of spontaneous neoplasms of the respiratory tract in this species than in those animals where chronic pulmonary inflammatory processes are uncommon It will be interesting, indeed, to see whether, as a late manifestation, there is an increase in the number of now relatively rare epithelial new growths in the respiratory tract of man.

The conception that pulmonary tumors in mice are stimulated by chronic pulmonary infections has no longer been widely held, since the precise studies of Grady and Stewart in tracing the evolution of these tumors in otherwise healthy mouse lungs (36). Influenza virus produces extensive epithelial proliferation in mouse lungs, but, in experiments conducted by Steiner and Loosli (43), lung tumors were not more frequent in mice previously infected with this virus than in uninfected controls The mice used for these experiments were young adults, and the tests leave open the question of whether the proliferative stimulus of the infections might have exerted an effect if they had been given later in life, when mouse lungs begin to bear tumors. One might also inquire whether the epithelial proliferation brought about by influenza virus creates a soil in which cancer might develop more easily upon subsequent stimulation by a chemical carcinogen. A test to explore this possibility was conducted by Campbell (44), with negative results, in mice exposed to influenza virus and subsequently allowed to inhale a dust containing coal tar over long periods of time

Influenza has not stood alone among chest diseases that have been suspected of playing a role in lung cancer. So great an authority as Ewing (45) made the statement in his textbook on neoplastic diseases that tuberculosis is the chief etiological factor in lung cancer. While it is true that occasional cases of cancer arising from the walls of tuberculous

cavities have been described, and in these instances the tuberculous process can be considered to have prepared the soil for the malignancy, the many cases of lung cancer without evidence of tuberculous infection make it difficult to associate the two diseases. But the concept that various pathologic changes, not in themselves neoplastic, may play some role in subsequent neoplastic developments, holds much that is thought-provoking. Adenocarcinomas of the lung tend to be composed of cells bearing some resemblance to those that normally line the bronchial passages, but the majority of lung tumors in man are anaplastic, undifferentiated, or frankly squamous. The squamous cell cancers are composed of cells that resemble skin tissue. Since no such tissue exists in healthy lungs, alteration (metaplasia) must occur in pulmonary epithelium in order to provide cells that could give rise to squamous cell cancers. As will be discussed later in this chapter, polycyclic hydrocarbon carcinogens cause extensive metaplasia of pulmonary epithelium, and a diversity of tumors have arisen from such metaplastic tissue under experimental conditions. Patches of squamous metaplasia are commonly seen in human lungs that have been the seat of chronic infections or irritations (46) and are found in animals deficient in Vitamin A (47). Such changes are found only inconstantly in lungs that are the seat of carcinoma and hence cannot be recognized as precancerous. Squamous metaplasia may be widespread in the lungs of old rats with chronic pulmonary infections, but cancer has not been found in such lungs (48). Nevertheless, the possibility cannot be entirely discounted that nonspecific metaplastic changes may predispose to cancer or provide tissue that may undergo further change in the direction of neoplasia upon subsequent exposure to other circumstances.

Exploration of dietary or metabolic factors from this point of view may reward the experimenter concerned with lung cancer, for nutritional studies have made interesting contributions to several fields of cancer research (49). In man, cancer is more common in the obese. In animals, the frequency of spontaneous tumors or of tumors induced by chemical carcinogens is decreased by caloric restriction. On the other hand, there is evidence that certain dietary imbalances lead to cancer. The frequency of cancer of the liver among some native groups in South Africa is thought to be consequent upon damage to that organ occasioned by diet deficiencies (50).

A decisive influence of diet upon carcinogenesis was discovered by Rhoads and Kensler (51), who demonstrated that the development of cancer in the livers of rats fed paradimethylamino-azobenzene could be prevented by adding yeast or liver extract to the food. Diets deficient in choline lead to fatty infiltration and cirrhosis of the liver, and tumors ensue. In the latter experiments, carried out with rats by Copeland and

Salmon (52), not only did hepatomas appear, but hemangio-endotheliomas and sarcomas developed at several sites—and, a finding of most direct interest to our present purpose, tumors were reported in the lungs. Indeed, these authors stated that autopsies revealed primary carcinomas of the lung in 38 per cent of their rats after eight to ten months upon the choline-deficient diet, and it would appear that this statement referred to tumors in nineteen animals. The lesions were described as nodular and composed of masses of anaplastic oval cells with numerous mitoses. Metastases were not mentioned. The neoplastic character of the growths was not tested by transplantation. No such lesions were observed among litter-mate control animals fed the same diet but given supplements of choline. Bronchiectatic cavities lined by metaplastic epithelium were found in the test rats. If the lesions interpreted as tumors were in fact such, and not simply nodules of metaplastic epithelium such as described in rats by Passey (48), then these experiments of Copeland and Salmon have large importance.

It will be recalled that mention was made of the increased frequency of mammary tumors in mice harboring the mammary tumor agent and injected with estrogens. The large literature on hormones in relation to cancer has been recently reviewed by Gardner and his associates (53). Long-continued administration of estrogens leads to cancer of the uterus in rabbits, cancer of the cervix and interstitial cell tumors of the testis in mice, and renal tumors in hamsters. Although it is possible that these hormones possess some primary carcinogenic property, their tumorigenic action may be less direct. In intact mice, estrogens cause thickening of the epithelium lining the cervical canal, with consequent stasis and infection that may play a role in bringing about the tumors that later appear, for estrogens fail to induce cancer from cervical tissue grown aseptically in subcutaneous sites. The impression grows that estrogens serve as developing agents, or as co-carcinogenic stimuli for a variety of neoplastic potentialities possessed by different strains of animals. Mice prone to develop leukemia exhibit an increased frequency and accelerated rate of appearance of this disease following administration of estrogens, and these effects can be negated by testosterone. Other families of mice, prone to develop pituitary adenomas, acquire these tumors more quickly and more frequently if estrogens are given. The fact that uterine tumors can be elicited in guinea pigs by administration of estrogens and that this effect can be antagonized and prevented by simultaneous injections of progesterone, indicates that the endocrine balance of the animal is involved, a view supported by the development of adrenal tumors after gonadectomy of young mice. The greater frequency of lung cancer among men as contrasted to women has suggested to many that endocrinological techniques may contribute to the understanding of this disease.

All these general considerations have been offered as a setting against which to view the more direct studies that have been attempted upon the specific problem of lung cancer. Subsequent chapters of this volume will describe the diversity of types of primary lung cancer encountered in man. Not only do these present differing clinical, surgical, and pathologic aspects, but the general categories may have differing etiologies. The investigator must therefore bear in mind that what he learns about one type of lung tumor may not apply to another, just as what he learns from experiments upon one species of animals may not apply to another. Recent reviews of experimental studies of lung tumors have been published by Stewart (54) and the author (55). These contain extensive bibliographies upon the subject, and the reader is referred to them for documentation of statements to follow.

The great majority of experimental studies of lung tumors have been conducted with mice, and center around the type of lung tumors common in that species. Wells, Slye, and Holmes (56), in examining 2865 cases of spontaneous lung tumors in mice, found epidermoid features in only seven. The remainder were adenomas, some of which had undergone cancerous evolution. In 104 cases, there were metastases outside the lungs. In thirty-three cases there were sarcomatous features. The development of sarcomatous elements (which can include bone) from adenomas is curious. Adenomas in mice commonly arise in the alveoli and lie close beneath the pleura (Fig. 1). They are discrete, compact nodules com- [illegible]

Their incidence can be reduced by caloric restriction (49). In proportion to their spontaneous incidence in the various strains examined, the rate of appearance and the eventual number of these pulmonary adenomas can be augmented by exposure to carcinogens. Extensive experimentation has demonstrated this effect following intravenous or subcutaneous injection of pure carcinogenic polycyclic hydrocarbons, or after intraperitoneal, oral, or intranasal administration of urethane, and even after repeated application of coal tar to the skin. Intravenous injection of either nitrogen mustard or sulfur mustard increases the incidence of these growths.

Discovery of the action of urethane, a water-soluble compound of small molecular size, is of unusual interest, for the polycyclic carcinogens, such as benzpyrene or dibenzanthracene, can induce tumors of many tissues, whereas urethane exhibits a carcinogenic action almost exclusively in the lungs. There is evidence to indicate that the number of pulmonary adenomas induced by it can be altered by substances thought to influence

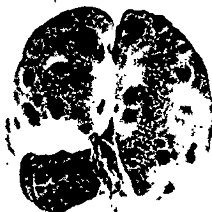






Fig 1. Multiple pulmonary adenomas in the lungs of a mouse Characteristically, they lie close beneath the pleura (From Grady and Stewart (36))

Fig 2 Pulmonary adenoma in the lung of a mouse It is composed of cuboidal and columnar cells in papillary glandular arrangement with little stroma Slightly enlarged from 200× (From Grady and Stewart, *ibid*)

Fig 3 Cross-section through a 10 mm mass resulting from transplantation of a tumor induced by methylcholanthrene from embryo lung tissue. Sections of the *original growth showed carcinomas of three distinct morphologic types* All grew in the transplant, as can be seen here The growth occupying the middle of the slice consists of thick septae of fibromatous appearance covered with cuboidal epithelial cells, as higher magnification showed The clefts between the septae are small *Toward the left there is a carcinoma composed of transitional* epithelium heaped up into a layer many cells deep On the right there is a squamous cell carcinoma. 17×

ucleic acid synthesis; the number is decreased by administration of odium desoxyribonucleate or thymine, and augmented by administration f adenine or aminopterin (57, 58)

Mating mice from a strain having a high frequency of pulmonary

eptibility to these tumors is not dependent upon a single gene but is ssociated with multiple factors, and he traced these to a particular chromosome of the mouse. He then conducted the following experiment (59)

Many tissues can be successfully transplanted from one individual to nother in a genetically homogenous strain of mice, but not to animals of another strain If individuals from two pure strains are mated, however, tissues from either parent strain will grow when transplanted into he offspring Heston mated individuals from a strain having a high requency of pulmonary adenomas to individuals from a strain having a very low incidence of these tumors Into the offspring of these matings, he transplanted lung tissue from each of the parent strains, placing the graft from the high tumor parent in one side and the graft from the low tumor parent into the other side of the new host He then injected a carcinogen, dibenzanthacene, intravenously into the animals bearing these grafts Many pulmonary adenomas arose in the grafts from the high tumor strain Very few arose in grafts taken from the low tumor parents This ingenious experiment demonstrated that factors determining susceptibility to these tumors reside in the lung tissue itself

A possible explanation for what these factors may be is suggested by some experiments with urethane So sensitive is mouse lung tissue to urethane that when pregnant mice are given this compound, pulmonary adenomas develop in their offspring (60) and can be detected in the lungs of baby mice as early as three days after their birth (61) In searching serial sections of lungs of baby mice born from untreated mothers, I have been impressed by the occasional presence of tiny nests of cells resembling adenoma cells in babies from a strain having a moderate incidence of adenomas in old age, whereas such cells were not evident in the lungs of babies from a strain that rarely develops adenomas (55). These observations would support a view that the development of pulmonary adenomas may depend upon stimulation of specific cells possessed in differing numbers by different individuals, and could afford an anatomical answer to the riddle of why one individual develops a tumor while another does not Observation of the cells in question in the very young suggests a possible explanation for the sarcomatous elements that not infrequently appear in the metastases (56) or transplants (62) of adenomas. Pulmonary adenomas in man often have components from two germ layers, and it

has been thought that such tumors owe their mixed character to origin from nests of cells having embryonic developmental potentialities (63).

But pulmonary adenomas are relatively uncommon in man and constitute only a small fraction of the human lung tumor problem. Attempts have been made to produce experimentally types of lung cancer common in man but until recently these have met with little success (for bibliography see Ref. 55). In 1924, Moller claimed to have found squamous cell carcinoma in six of 24 rats after long-continued painting of tar onto the skin In view of Passey's subsequent demonstration (48) of the frequency of extensive squamous metaplasia in the lungs of old rats, one may doubt that the changes described by Moller were carcinoma. Coal tar injected through the chest wall into rabbit lungs or instilled intratracheally into mouse lungs failed to evoke cancer, though the intratracheal method is said to have yielded an adenocarcinoma in a guinea pig. Methylcholanthrene in olive oil injected intratracheally into mice evoked sarcomas rather than carcinomas (64) but a Finnish author, Niskanen (46), claimed that he observed squamous cell carcinomas in rat lungs after intratracheal injection of dibenzanthracene in olive oil. His photographs suggest that at least one lesion may have been neoplastic rather than merely metaplastic, but none were transplanted, and the claim that they were in fact cancers must be viewed with some reservations. Intrapulmonary injection of the powerful pure carcinogens methylcholanthrene, benzpyrene, dibenzanthracene and 9,10-dimethyl-1-2-benzanthracene dissolved in paraffin have provoked sarcomas and adenomas in mouse lungs, but completely failed to elicit any carcinomas (65).

The first indubitable experimental production of a squamous cell carcinoma of the lung was accomplished in 1937 by Andervont (66), who coated threads with dibenzanthracene and drew them through the chest walls of mice. He cut each thread where it emerged from the body wall and thus left a piece in the lung. By successfully transplanting the growths serially in new hosts, Andervont established the truly neoplastic nature of a squamous cell cancer induced in this way.

Carcinomas resembling types seen in man have been induced from lung tissues removed from mouse embryos and transplanted along with methylcholanthrene (67) or dibenzanthracene (68) into the thigh muscles of adult animals of an inbred strain (Figs. 3–7). With the use of this procedure (the "tissue transplant technique"), lung tissue has yielded squamous cell, transitional cell, and anaplastic and alveolar cell carcinomas, and the neoplastic nature of each of these types of growths has been established by successful transplantation These experiments were undertaken to learn whether fetal lung tissue possessed the potentiality for neoplastic change, or whether such liabilities were acquired later in life, perhaps due to acquisition of neoplastic viruses. The diverse cancers that

resulted leave little ground to suppose that the generality of lung tumors can be due to neoplastic viruses entering the organism in postnatal life

A finding of particular interest was the early occurrence of metaplasia in implants of pulmonary epithelium exposed to carcinogens. Figure 8 shows a section of the wall of a bronchial structure in such an implant On one side, the cells have heaped up into several layers of transitional epithelium, on the other they have formed a layer of stratified squamous, but not keratinizing, epithelium In many other implants, fully developed *squamous metaplasia* with production of keratin was observed Transplantation of such tissue to new hosts within 80 days following the original transplantation of fetal tissue failed, demonstrating that it was merely metaplastic and not neoplastic After 80 days, successful transplants of cancers composed of each of these types of metaplastic cells were achieved. These findings indicate that neoplastic change can supervene in cells at various stages of metaplasia, and that once the neoplastic change occurs the metaplasia proceeds no further.

These considerations may bear upon the diversity of histologic appearances encountered in cancer of the lung in man, it having been often remarked that sections from different areas of a human lung cancer can reveal very different types of malignancies (69). This occurred in growths induced from lung tissue through exposure to carcinogens by the tissue transplant technique (Fig 3). In subsequent serial transplants of such growths to new hosts it was occasionally possible to recognize differences in the gross and to separate the tumor into its component parts, transplanting each individually (Figs 4–6). This supports the impression, gained from study of the original tumors, that neoplasia arose in several foci, and that the varied character of the original tumor was due to the advent of malignant change in cells at different stages of metaplasia

Mention has been made of the induction of adenomas in mouse lungs following intravenous, subcutaneous, percutaneous, and oral administration of carcinogens To what has already been said may be added the observation of primary hemangio-endothelioma of the mouse lung after subcutaneous injection of ortho-amino-azotoluene (70) These facts make plain that thinking upon the role of carcinogens in lung cancer cannot be limited to their more obvious portal of entry through the respiratory tract Nevertheless, data available from occupational lung cancer experience focus attention upon materials that enter the lungs by inhalation (27), as do the epidemiological studies on smoking and urban air pollution discussed in another chapter of this volume

In a series of experiments extending over many years, the late Argyll Campbell exposed several thousand mice to inhalation of various materials. A table taken from his last paper (28), in which he summarized his find-



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ings, is reproduced in Table I. The animals used for Campbell's experiments were not of the highly inbred strains now readily available, and the frequency of lung tumors varied substantially among his control groups. From his numerous papers, it would appear that the majority of lung tumors that he encountered were adenomas or adenocarcinomas, and in his protocols he distinguished between "simple" and "malignant" tumors, often finding a higher percentage of the latter among mice that had been exposed to various dusts. He published several photographs, however, to illustrate tumors diagnosed as oat-cell cancers (28). In general, his procedure was to use a group of 150 mice, of which 75 were preserved as controls and 75 were exposed to a test material, the animals in each category being divided up as to color and sex. The test mice were exposed in a closed chamber to a cloud of dust once an hour for six times a day on five days each week for a year. They were allowed to complete their span of life and histological sections were made of their lungs (71, 72).

From Table I, it can be seen that a striking increase in the frequency of tumors occurred in an experiment in which mice were exposed to dust swept from tarred roads, the rate being 74 per cent in test mice as contrasted to only 8 per cent in controls. A lesser incidence (47.3 per cent) was found in a second experiment where the animals inhaled carbon monoxide in addition to the road dust, and this lesser rate was almost reached by mice allowed to inhale the dust after removal of "tar" by benzene. Only 13.1 per cent of mice developed lung tumors in a further experiment where the exposure was to dust swept from the same road

Fig. 4. The transitional cell carcinoma of Fig. 3, growing in a subsequent transplantation. (30×)

Fig. 5. Higher magnification of the tumor shown in Fig. 4. The transitional-type cells are being shed singly without formation of lamellated keratin. (175×)

Fig. 6. Tumor resulting from further transplantation of the growth seen in the middle of Fig. 3. In the older part of the mass there are numerous clefts separated by thick septae of connective tissue lined by cuboidal cells. The vigorously invasive edge of the growth consists of undifferentiated epithelial cells. (50×)

Fig. 7. Epidermoid carcinoma derived from embryo lung tissue exposed to methylcholanthrene. In contrast to the transitional cell carcinoma shown in Figs. 4 and 5, this growth formed large cysts filled with keratinized material. (35×)

Fig. 8. Illustration of stages of metaplasia in the wall of a bronchial structure growing at an intramuscular site of implantation of embryo lung tissue, together with methylcholanthrene. At the center, columnar bronchial epithelium is thrown into redundant folds. On the left, there is a thick layer of transitional epithelium. On the right, metaplasia is further advanced toward epithelium of squamous character. (125×)

(Figs. 3 to 8 are reproduced from Smith (67).)


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theory that local anoxia might play some role in initiating neoplasia, he attempted an experiment to learn whether reduced atmospheric oxygen pressure augmented the incidence of lung tumors. He concluded that it did so, though his data in this respect were few and unimpressive (72).

Campbell's experiments were conducted in London in the nineteen-thirties soon after Kennaway, working in the same city, had found carcinogenic activity in the products of pyrolysis of many organic substances (73) Campbell tested the effect of exposing mice to exhaust gases from gasoline engines, housing the animals in a chamber into which such gases were introduced on five days a week throughout their lives. In a similar experiment, he maintained mice throughout their lives in a chamber into which the smoke from 12 cigarettes was puffed five days a week. In the experiment with cigarette smoke and in one of two experiments with exhaust gases, lung tumors were somewhat more frequent in exposed groups than in controls, but the numbers of tumor-bearing mice were small (74). There was no unusual frequency of lung tumors in mice exposed daily over a period of 16 months to tobacco smoke, in experiments conducted by Passey (75) Also, Lorenz and Stewart (76) exposed mice with a high spontaneous incidence of pulmonary adenomas to inhalation of tobacco smoke several hours a day for 250 days, without finding any increased frequency of lung tumors In their experiments, the tobacco was burned in an automatically puffed pipe. Recently, Essenberg (77), utilizing the same strain of mice, exposed animals daily over the course of a year to smoke from automatically burned cigarettes. In this experiment, an increased frequency of lung tumors was recorded in the exposed animals, but the tumors illustrated were adenomas rather than tumors of the types common in man In Essenberg's experiments, it would appear that the cigarettes were not puffed, but were burned by continuous suction. Such a procedure may have resulted in quantitative or qualitative differences in composition of the smoke as compared with that encountered in ordinary smoking.

The temperature at which tobacco burns was found by Ashley Cooper and his associates to range from 370° to 700°C., depending upon the vigor of the smoking These authors recalled the importance of high temperature in the formation of carcinogens in coal tar (78) Smoke condensates prepared by them from tobacco burned in automatically puffed pipes, produced a skin cancer in only one out of 50 mice after repeated application to the skin Various preparations of tobacco "tars" have been tested by a number of investigators by direct application to the skin, with tumors resulting in some studies and not in others Reviews of these studies, containing extensive bibliographies, have been published by Flory (79), and by Wynder, Graham, and Croninger (80). The first tumor produced experimentally by a condensate of tobacco smoke, a carcinoma

TABLE I

SIGNIFICANCE OF INCREASE IN INCIDENCE OF LUNG TUMORS IN DUSTED MICE *

Experiment	Percentage Lung Tumor Incidence		Ratio of Difference between E and C to Standard Error of Difference	Significance of Increase Due to Dust
	Dusted Mice (E)	Control Mice (C)		
Tarred road dust (1)	74.0	8.0	7.2	Highly significant
CO + tarred road dust	47.3	7.5	4.1	
$Al_2O_3 + SiO_2 + Fe_2O_3 + CaCO_3$	19.4	0.0	3.6	
Fe_2O_3	32.7	9.6	2.9	Definitely significant
Czechoslovak dust (2)	20.3	2.1	2.8	
Tar-free road dust	44.8	20.0	2.7	
Tarred road dust (2)	13.1	1.4	2.6	
Diluted "nickel" dust	29.8	12.5	2.2	Some significance, but near borderline
Czechoslovak dust (1)	11.5	1.7	2.2	
Bituminous coal	12.1	1.9	2.1	
SiO_2 + "nickel" dust	17.4	5.0	1.8	An increase, but might easily be due to chance
$SiO_2 + Fe_2O_3$	19.4	9.6	1.5	
Carbon, exhaust soot	33.3	20.0	1.5	
$Al_2O_3 + SiO_2 + Fe_2O_3$	15.8	9.2	1.1	
Steel grindings	13.6	7.7	1.0	
Anthracite coal	9.1	7.0	0.4	No increase of any significance
Coal soot	20.0	20.0	0.0	

* From J. A. Campbell, "Lung Tumors in Mice and Man," *Brit. M. J.*, 1:179, 1943

five years after the tarring had been done, the first test having been done with sweepings made soon after the tarring of the road (71). Somewhat elevated lung tumor rates were recorded among mice that had inhaled ferric oxide dust, pitchblende ("Czechoslovak") dust, and certain other materials as recorded in his table. The pitchblende dust came from the Czechoslovakian mines where cancer of the lungs has been observed as an occupational hazard for miners (1). Inspection of the table reveals that higher frequencies of lung tumors were recorded in mice exposed to nearly every one of the dusts tested, and Campbell appears to have been impressed by this to the extent of speculating that the tumors found in control mice might have resulted from inhalation of dust from the sawdust used for their bedding. He attempted to ascertain whether the presence of any sort of relatively insoluble material in the lungs might be associated with an increased frequency of lung tumors, but found no dependence of tumor incidence upon the degree of dust deposit. On the

revealed various alterations, of which three may be singled out for comment. Sebaceous glands disappeared and nucleoli of epidermal cells enlarged within four days, while after ten days the painted area became bald (85) Subsidiary tests of a variety of fractions derived from petroleum or from coal tar disclosed that these changes followed exposure to fractions known to be carcinogenic as a result of prior long-term tests for actual tumor induction Studies of dilutions of such samples revealed that their relative carcinogenic potency could be estimated by counts of the number of sebaceous glands per centimeter four days after application of test material, the relationship being inverse, *i e.*, the fewer the glands, the more potent the sample. In human volunteers, nucleolar enlargement occurred in skin painted with coal tar, benzpyrene, and a high-boiling petroleum fraction known to be carcinogenic for mice, rabbits, and monkeys (86) Cigarette smoke condensate elicited a lesser effect in this direction and did not suppress sebaceous glands except in one of four volunteers

Fractions of cigarette smoke condensates prepared by Alvin Kosak and others (87) have been tested upon mouse skin Counts of the number of sebaceous glands after four daily applications of these samples focused attention upon two of them as being presumably carcinogenic These two fractions, suspected of possessing carcinogenicity on the basis of the early skin changes, proved, in experiments recently completed, to be the ones that elicited skin tumors in subsequent long-term tests upon mice and rabbits

It is interesting to recall that the identification of a pure chemical carcinogen among the multitude of compounds present in coal tar was enormously facilitated by the distinctive fluorescence of benzpyrene, "the thread that led through the maze." From the experience described, it would appear that observations upon early changes in the skin afford a similar "thread" to guide searches for carcinogenic components in petroleum derivatives or cigarette smoke condensates For investigators concerned with studies of carcinogens formed by pyrolysis, Kennaway's classic paper remains a cornerstone for thought (73)

But identification of a compound capable of eliciting cancer when applied upon the skin is not *ipso facto* evidence that it can exert a similar action upon the respiratory tract Not only do these [illegible]

into the lungs is widely dispersed Earlier in this chapter we commented upon unsuccessful efforts to induce carcinoma by injection of potent carcinogens into the lungs In an effort to obtain long-continued apposition of a test substance with the lungs, Hueper (88) introduced powdered nickel intrapleurally into rats He selected this metal because of the high

upon a rabbit's ear, was reported in 1930 by Roffo, who subsequently published a series of papers describing further experiments in which he observed papillomas and carcinomas upon the skin of that species after painting with tars obtained by heating tobacco in an iron vessel, or by condensing smoke from tobacco burned in a pipe (81) Flory (80), working with smoke condensates from tobacco burned without puffing in pipes under continuous suction, elicited papillomas or "carcinoids" on the skins of 22 out of 24 rabbits. Mice were much less responsive to this material, skin tumors appearing in only three out of 22 of them Cigar smoke tar elicited papillomas and carcinomas from the skins of rabbits, but not of mice, in tests reported by Schurch and Winterstein (82). A high frequency of tumors upon mouse skin has, however, been described by Wynder, Graham, and Croninger (79), who worked with smoke condensates from automatically puffed cigarettes. They reported papillomas on the skin in 59 per cent of 81 mice, and in 44 per cent, carcinomas developed. These authors attributed the high carcinogenic potency described for their material to intensive and prolonged dosage. The average temperature observed by them in puffed cigarettes was 682°C, but temperatures up to 966°C. were recorded.

The chemical nature of the carcinogenic material present in tobacco smoke condensates, where such has been demonstrated, is unknown Claims have been advanced for the identification of benzpyrene in puffed smoke from cigarettes (82) and in smoke from cigarette paper (83), but these claims are based wholly upon observations of spectroscopic bands The chemical compounds that have been positively identified in tobacco smoke comprise a considerable list (84), but no known carcinogens are among them except arsenic, which presumably derives from pesticides applied to tobacco crops Cigarette smoke is, indeed, such a highly complex mixture that substantial practical difficulty surmounts the production of subfractions in sufficient quantity for biological tests intended to search for specific carcinogenic compounds. In the original effort to identify a pure chemical carcinogen in coal tar, more than a ton of material was used before success was achieved In the case of relatively crude fractions of materials containing low-potency carcinogens, or high-potency carcinogens in small amounts, biological tests by repeated application to the skin of mice must often continue for periods approximating a year or even longer before tumors can be observed. The time required, and the relatively large amounts of samples needed for such a procedure, present serious obstacles to research. In our studies of this problem, therefore, a first objective was to attempt to learn whether any early changes occurred in the skin that might serve as guides to indicate fractions possessing potential carcinogenic activity

Examination of mouse skin painted with cigarette smoke condensates

carcinogen adsorbed upon charcoal particles The negative outcome of the tests is the more interesting, for Steiner has shown that the carcinogenic activity of benzpyrene, measured by subcutaneous injection, is lost when that compound is injected adsorbed upon carbon black (94)

Recently, Vorwald (95) has demonstrated in rats allowed to inhale beryllium salts that an inorganic dust can enter the lungs of animals by inhalation and there produce cancers of types resembling some of those seen in man. Both adenocarcinomas and epidermoid cancers were induced in this way. A severe pneumoconiosis has been recognized in human beings exposed to beryllium dusts, but as yet no cases of cancer have been attributed to such exposure. Tumors have been described by Lisco and Finkel (96) in the lungs of rats that had inhaled radioactive cerium, and these, in photographs yet unpublished, appear to have been epidermoid carcinomas Their finding is of particular interest in view of the frequency of lung cancer, notably epidermoid growths, among workers in mines bearing radioactive ores (1) We have earlier in this chapter commented on Essenberg's report of an increased frequency of lung tumors in mice [illegible]

fidence in the use of lower animals for evaluation of the potential carcinogenicity of inhaled substances

In conclusion, the several experiments cited to show that inhalation of agents from the external environment can incite lung tumors in two species of lower animals indicate a promising approach for experimental investigations of possible causes of this disease. It is curious that potent carcinogenic hydrocarbons instilled or injected into the lungs in solution in oil or in soft paraffin have almost invariably failed to elicit tumors (carcinomas) of the tissue (epithelium) lining the surface of the respiratory tract, but have instead caused tumors (sarcomas) of the deeper tissues. These facts argue that carcinogens which are presented to the lungs in solution pass readily away from or through the bronchial epithelium and affect deeper structures. Indeed, when the normal relations of the lung are disturbed, as happens in the tissue transplant technique referred to above, then solutions of carcinogens readily elicit carcinomas from pulmonary epithelium These considerations may explain why carcinomas were obtained by Andervont when he inserted into the lungs threads coated with dibenzanthracene, for the chemical then existed as crystals, and it may be presumed that some crystals were arrested by portions of the lining epithelium. In planning experiments on lung cancer, large rewards may therefore be anticipated from careful consideration of the physical state in which test materials are presented to the lungs Industrial physicians and hygienists are well aware that the particle size of

frequency of respiratory tract cancers among employees of a nickel refinery. Tumors resulted in occasional rats treated in this manner, but they were sarcomas rather than carcinomas and sprang apparently from the chest wall. In unpublished experiments, we have implanted nickel (average particle size 0 9 μ) intramuscularly into mice together with lung tissue obtained from mouse embryos. The lung tissue grew well, the metallic particles being intimately admixed with it. Two adenocarcinomas resulted This procedure, the "tissue transplant technique" (68), affords a convenient means of testing materials for carcinogenic action directly against a variety of tissues, but involves highly artificial conditions which do not simulate those encountered in nature. Since the majority of evidence for environmental factors in lung cancer points toward inhalation as the *mode of entry, inhalation techniques are therefore of particular* interest to the experimenter

Campbell's experiments upon the effects of inhalations of sweepings from tarred roads have already been discussed An increased frequency of adenomas was observed by McDonald and Woodhouse (89) in the lungs of mice that they exposed to inhalation of dust collected from the air of an English city. These experiments as well as the epidemiological data presented in an ensuing chapter have focused attention upon air pollution as a possible environmental factor in lung cancer. Extracts of dust collected from the air of eight cities in the United States have produced cancer at the sites of injection in mice (90). Condensates of exhausts from gasoline and diesel engines have produced cancer when applied repeatedly to the skin of mice. In these later experiments, conducted by Kotin (91), the powerful carcinogen 3,4-benzpyrene has been identified in exhausts from both types of engine. This carcinogen is known to result also from the destructive distillation of coal. The amounts of benzpyrene in the air of several English cities have been measured by Kennaway and Waller (92), who have calculated that a man living in London for seventy years would inhale from the city air about 12.5 mg of benzpyrene, more than six thousand times the amount required to produce a fatal cancer at the site of injection into a mouse Like many other polycyclic hydrocarbons, benzpyrene has increased the frequency of pulmonary adenomas in mice after intravenous injection (54), but no experimental tests have been made upon the effects of inhaling it Indeed, the only experiments thus far reported upon inhalation of a powerful pure polycyclic hydrocarbon carcinogen (9,10-dimethyl-1,2-benzanthracene) have yielded negative results (93) This latter compound is the most potent carcinogen known, as judged by its ability to induce cancer when applied to the skin of mice, yet in the experiments *described no tumors appeared in the* lungs of mice that had been allowed to inhale large quantities of it. The animals in these tests inhaled the

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noxious dusts plays a large role in determining the site of tissue reaction in the lungs. Thus, the small particles of siliceous dust penetrate and exert their pathologic effects on the deeper tissues, whereas the larger fibers of asbestos are arrested in the bronchioles and produce a wholly different pathologic picture. The known facts gleaned from experimental studies of silicosis and asbestosis may prove of much value in future inhalation studies of materials suspected to cause cancer of the lungs

In retrospect, one cannot fail to be struck by the multiplicity of factors that have been found to have etiological significance in cancer. Upward of two hundred chemicals ranging from elaborate organic compounds to simple metals (97) have been shown to induce cancer in one or another species Viruses, dietary deficiencies, hormonal imbalances, radiant energy, have evoked this disease. If there is a single, specific biochemical lesion that sets in motion the unchecked multiplication of cells that we speak of as "cancer," then it can be triggered by many agencies The fact that "spontaneous" tumors generally arise late in life suggests that cancer may occur as a result of biochemical difficulties within aging cells or in mechanisms that govern the orderly cellular society of differentiated organisms. There can be little wonder that the complex chemistry of living cells or the complexity of anatomical organization of many different cell types into properly functioning tissues and organs can be disturbed by a host of differing agents The diversity of agents that have been found to provoke tumors make it difficult to escape the view that "malignant" change is one of the fundamental types of response to injury. That injuries leading to cancer may be subtle and particular is made clear by the minute quantity of some carcinogens needed to evoke them and by loss of carcinogenic action upon small changes in the molecular structure of offending agents. But, when confronted by noxious influences, what is there for a cell to do but die, or make more or less recovery, or respond with enhanced vigor, even to the extent of unruly growth? These three patterns of response are familiar enough in the lives of nations and individuals Recognition of their existence upon the cellular level may remove some of the sense of confusion attendant upon the multiplicity of carcinogenic stimuli

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3

Environmental and Occupational Factors in the Development of Lung Cancer

E. Cuyler Hammond
and Willard Machle

INTRODUCTION

One of the most dramatic things that has happened to mankind during the last century is the tremendous drop in age-specific death rates. The age-standardized rate for adult white males in the United States declined from 2026 per 100,000 in 1900, to 1635 in 1930, to 1333 in 1950 The corresponding figures for adult white females are 1867 in 1900, 1363 in 1930, and 883 in 1950 Practically all of the decline has been in death rates from infectious diseases, particularly diseases of the respiratory system. In sharp contrast with the general picture is the phenomenal rise that has occurred in lung cancer death rates, particularly among males It is significant that there is perhaps only one other important disease (coronary heart disease) that increased in age-standardized death rate to any great extent during the same period of time

Lung cancer was apparently a rare disease in 1900 As recently as 1933, only 3410 deaths (2252 male and 1158 female) were reported from this cause in the United States In contrast, 21,582 lung cancer deaths (17,821 male and 3761 female) were officially reported in this country in 1952. It is estimated that the total reached 25,000 in 1954 Part of the rise is accounted for by an increase in the number of old people in our population. However, age-standardized lung cancer death rates rose as follows for white males from about 0.7 per 100,000 in 1914 to 4 6 in 1933 and 22.0 in 1952, and for white females from about 0 6 in 1914 to 2 3 in 1933 and 4 4 in 1952. (See Fig 9) It is thought that most if not all of the rise occurred in the epidermoid and undifferentiated forms of the disease and that there was little rise in the adenocarcinoma form (1). At

LUNG*CANCER DEATH RATES**AMONG WHITE MALES AND FEMALES
UNITED STATES, 1914-1954

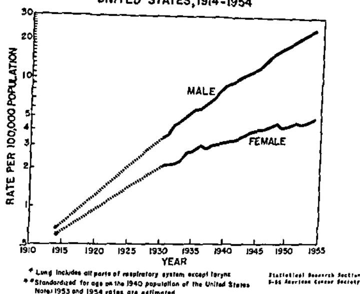


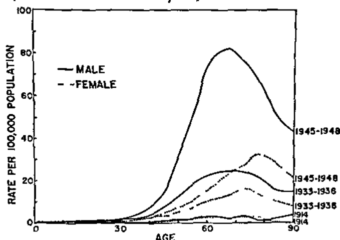
Fig 9

the present time, the adenocarcinoma form, which is the rarer type, accounts for a much larger proportion of the female cases than of the male cases

Up until a few years ago there was considerable debate as to whether the reported rise in lung cancer death rates was real or whether it was due simply to better diagnosis and more complete reporting It is now generally agreed that while some of the apparent increase was probably due to improved diagnosis, a real and substantial increase has actually taken place (See Dorn (2) and Horn (3).)

At the same time that the rates have been increasing, a change has occurred in the shape of the age distribution curves. (See Fig. 10 (4).) Unlike most other forms of cancer, the rates decline after a certain age However, when an analysis is made of lung cancer death rates of men born in the same decade, it is found that the rates continue to rise steadily with advancing age (See Table II (5–7)) Men born in each successive decade have had higher lung cancer death rates than their predecessors when they reached the same age. These trends certainly suggest that some new factor or factors causative for lung cancer were introduced into the human environment (or else greatly increased) during the past

LUNG CANCER DEATH RATES, BY AGE & SEX
White Population of the United States, 1914, 1933-1936 and 1945-1948



SOURCE NATIONAL OFFICE OF VITAL STATISTICS,
BUREAU OF THE CENSUS

Reference #4 Hammond E Cuyler Smoking in Relation to Lung Cancer, A Follow-up Study, Connecticut State Medical Journal, January 1954 Issue, Vol XVIII No 1 page 3 (Reprinted by Permission of the Editor of the Connecticut State Medical Journal)

Fig 10

TABLE II

White Male Cohort Born in	Respiratory Cancer Death Rates per 100,000 at Attained Ages				
	35–44	45–54	55–64	65–74	75–84
1855–1865				26 4	51 7
1865–1875			20 1	53 8	109 1
1875–1885		10 7	47 4	119 4	
1885–1895	3 4	23 8	95 9		
1895–1905	6 0	39 1			

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and females, the relative difference between urban and rural rates is greater among males. There is some doubt as to whether these differences are

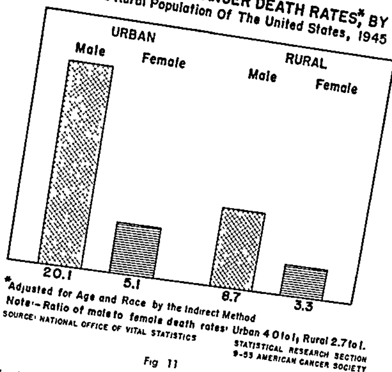


Fig 11

real or whether they are due in part at least to more adequate diagnosis in urban areas and to peculiarities of the reporting system It should also be noted that reported death rates for most important diseases are somewhat higher in urban areas than in rural areas.

The lung cancer mortality picture as just described for the United States is essentially the same for most other countries where accurate statistics are available. However, the levels of rates vary from country to country For example, age-standardized lung cancer death rates are substantially higher in Great Britain than in this country.

ETIOLOGY

...t the present state of our knowledge of the nature of normal and neo...tic growth, it is unlikely that we will soon acquire any very direct ...ence of the exact nature and mode of action of many specific car...genic agents that may be operating to produce lung cancer in man, ... factors that may increase susceptibility to this disease. Absolutely ...n proof that a specified agent causes lung cancer in man could only ...tained by experimenting with human beings. Such experimentation

is not feasible Nevertheless, evidence can be adduced in several ways that permits us, at least in certain instances, to draw conclusions with a reasonable degree of certainty.

Epidemiological Studies

In their simplest form these serve to measure the degree of association between rates for lung cancer and exposure to a suspected agent The finding of an association leads to two alternative hypotheses Either, 1) the suspected agent is a causative factor for lung cancer, or 2) the suspected agent is incidentally associated with some other factor or factors which are causative for lung cancer Lack of evidence in support of the second hypothesis serves in some measure as evidence in support of the first Additional studies can offer evidence that helps to distinguish between these alternative explanations, such as quantitative relationship between magnitude of exposure and attack rates for lung cancer, finding of specific histologic types of lung cancer, associated time trends, shift of high attack rates to younger age groups, and evidence of the carcinogenicity of the agent for man in sites other than the lung Owing to the long exposure period (perhaps 15 years) apparently required for initiation of lung cancer in man, studies in attack rates following removal of the suspected agent are of limited value owing to the different life experience in the two periods

Animal Experimentation

The induction of tumors in experimental animals is a practice beset with pitfalls, the successful induction of a tumor in a mouse can of itself have little weight in estimating the carcinogenicity of a material for man We do not know whether man is more or less susceptible to the action of carcinogens than are the inbred strains of mice usually employed Animal species vary widely in their response—even the most effective carcinogens for the mouse will produce no tumors in the monkey (9) Evidence for an etiologic role in the cases of environmental and occupational cancer is therefore limited at present to epidemiologic data exhibiting certain associations, patterns, and trends, and to the very dubious inferences which have been drawn from the experimental induction of tumors in animals by application of the suspected materials The weakness in the latter evidence has been discussed (10) A further complication is introduced by *the profound influence of the attributes of particle size distribution*, and the degree of adsorption of gases upon particles, in determining the effectiveness and locus of action of agents acting upon the lung Kotin (11) has shown that knowledge of the composition of pollutants at their sources may be misleading since a photochemically active atmosphere may produce new products of enhanced activity.

In most situations an estimation of any causal role for a suspected agent is further complicated by the difficulties entailed in evaluating the role of any individual agent as a carcinogen or co-carcinogen. Rusch (12), Berenblum (13), and others have pointed out that cancer experimentally induced by chemical agents is a process involving at least two stages, initiation and promotion. Instances of isolated exposure to a single specific agent are almost unknown Until such time as we are able to measure the specific roles of multiple agents in the genesis of what we may call "carcinogenic situations," and to determine the quantitative aspects of the role of each as inciter or promoter, we shall continue to operate in the areas of suspicion, possibility, and likelihood. It is in these realms that intuitive, first-person decisions are made. Limited evidence or mere association may be, for one person, an adequate basis for assignment of causal relationship, for another observer, the data may be quite inadequate. This problem has been discussed by Dorn (14) in relation to cancer and in its broader scientific aspects by Werkmeister (15) and Braithwaite (16).

AGENTS UNDER SUSPICION

In the search for environmental factors that might cause lung cancer, virtually the only substances that have come under suspicion are dusts, vapors, and gases inhaled by human beings. These may be divided into three general categories 1) inhalants to which workers are exposed because of their occupation, 2) general air pollution to which people may be exposed regardless of their occupation, and 3) tobacco smoking. They will be discussed in that order.

OCCUPATIONAL EXPOSURES

As a practical matter lung cancer associated with occupation is environmental in origin and entails no differing considerations except in the sizes and localizations of populations, and in the magnitudes of exposures involved. For thousands of years man has been mining the materials of the earth and using, refining, or processing them along with such other natural products as have come to his hand As a consequence, new materials have been formed or pre-existing substances have been altered in state. At times the naturally occurring elements have been concentrated to degrees unknown in nature, as in the cases of industrial metals and the metals of coinage. In a dozen or so important instances, elements have been processed to enable their use in extremely wide distribution upon the face of the earth, and eventually in the atmosphere as well. For example, thousands of tons of lead are mined annually to be redistributed as the weathered dust from paints and devices, and in the exhausts of

gasoline engines Uranium is mined, processed, and redistributed in the atmosphere as radioactive dusts and gases. In the past hundred years, man has added to his chemical environment a staggering number of agents, many existing for the first time

Concomitant with these developments in the Western world has been an increase in population, industrialization, and the growth of urban centers The consequence of all this has been to create a chemical environment like nothing that man has experienced before, both in the kind and magnitude of his exposures. This new chemical environment has been responsible, in some instances, for great increases in rates for known industrial diseases, and in others for the creating of new diseases

Certain industrial situations, where the exposure of men to a specific chemical agent is unique in kind or quantity, have at times exhibited unusually high attack rates for respiratory cancer among the exposed workmen (17) These age and sex specific rates may be very much higher than those for groups employed in similar industries that do not entail exposure to the identifiable and suspected agent There exists another less well-defined group of occupations, employment in which is associated with abnormally high attack rates for respiratory cancer, but in which the recognized potential exposures are either diverse or unde- [illegible]

(U238, U235, U234 and products) is the only one that has been indicated as a cause of respiratory cancer (18) "Bergkrankheit," as the Schneeberg lung cancer was called, is of special interest at this time as the first cancer attributed to radiation, and more significantly as an example of the dependence of biological science upon the general body of science for integrating concepts, general laws, and special tools essential to the understanding of etiologic relationships In the sixteenth century Agricola described a disease of the lungs with a high mortality rate in the miners [illegible]

years of work in the mines Of a mining population of 600 to 700 men, approximately 22 died each year of lung cancer Koelsch (20) reported 469 deaths of miners in the period 1875 to 1912, of which 276 were due to cancer of the lung A comparative study by Thiele, Rostoski, Saupe, and Schmorl (21) established that the disease was limited to the miners and only rarely affected other workers in the community

Exposure in the Erz Gebirge mines is mixed The principal ores of the Schneeberg are the sulfides and arsenides of nickel and cobalt, and at Joachimsthal the foregoing plus silver and a high content of pitchblende

and radium. The identification of natural radioactivity by Becquerel (22) did not occur until 1896, and knowledge of the carcinogenic effects of radiation was not available before the early 1900's. Therefore it is not surprising that conjectures as to causal associations for the then 300-year-old clinical entity were intuitively focused upon the materials that were substantively familiar to the minds of the generation. Principal among these were arsenic and cobalt. The consequence of this was that for many years exposure to cobalt and arsenic was considered to be the most important etiologic factor. Not until 1929 did the work of Loewy (23) and that of Sikl (24) in 1930, first present evidence that the radioactivity of the ores was the principal etiologic agent. Later reports of the occurrence of lung cancer among the processors of radium ores (Baader, Teleky, and Neitzel (25) have supported this position Lorenz (18) has questioned the importance of the role of radioactivity, basing his argument upon the failure to produce lung cancer in animals by x and gamma radiation. The experiments, however, were not pertinent since the exposure of the miners was to particulate and gaseous radioactive material, the particulates being capable of operating with high energy at point sources, and likely to be accumulated locally. More relevant are the experiments of Lisco (26) who produced lung cancer in rats by exposure to aerosols of radioactive cerium and plutonium.

The nature and magnitude of exposure in the Erz Gebirge mines has been incompletely defined. Ludewig and Lornser (27) reported the following composition. silicic acid, 51.00, alumina, 14.65; ferrous oxide, 7.15; lime, 12.86, magnesium, 3.20, cobalt nickel arsenide, 0 27. Radioactivity from uranium and its daughter products was measured in a variety of ways Results ranged up to 221 Mache units for the water in the working faces (Teleky (28)). One sample of water contained 3.44×10^{-4} millicuries of radium.

Chromates. K B. Lehmann (29) in 1932, Koelsch (20) in 1938, and Alwens and Jonas (30) in 1938 described cases of lung cancer among chromate workers in Germany and attributed the disease to exposure to chromates Machle and Gregorious (31) in 1948 reported their study of the mortality data for 1445 workers employed in the chromate industry in the United States. Among 193 deaths over periods of years (varying with the plants), 66 were from cancer and of these 63.6 per cent were from cancer of the lung This figure may be compared with that of 8 7 per cent in a control group of industrial employees In chromate workers over 50 years of age the mortality rate was up to forty times that for a comparable industrial group, and for workers under 50 years of age, seventy times the expected rate The median duration of exposure was 14 5 years, the ranges were five to 47 years The distribution of cases with respect to duration of exposure was about the same for European

and American cases. Studies by Baetjer (32) have included a systematic review of the literature, and a study in 1950 of incidence based upon hospital records. She reported the occurrence of cancer of the respiratory tract in 109 men in the chromate producing industry, and 11 cases in the chrome pigment industry. The inciting agent in the producing industry appears to be the monochromates, and in the pigment industry, the chromates of lead and zinc.

Chromium and its compounds enjoy wide use in industrial processes, in application to pigments and rust preventives, and as catalyst agents. Although chrome ulcers and dermatitis may result from the processing or handling of certain of these products, there is as yet no epidemiologic evidence for the occurrence among users of unusual rates for lung cancers. Since quantity and duration of exposure are important parameters in the induction of cancer, extensive epidemiologic studies will have to be done before any carcinogenic hazard to handlers of chromate products can be considered as more than a suspicion.

Nickel. Nickel carbonyl has been under suspicion as an inciter of lung cancer for many years. Recently, 52 cases of cancer of the nose or nasal sinuses and 93 cases of lung cancer have been reported from one plant in England (33). Data on the exposed population was incomplete and rates were not computed. Similar observations have recently been reported from a Norwegian nickel refinery by Løken (34), who saw three cases of lung cancer. The hazard does not obtain in all nickel processing plants. No cancers of the respiratory tract have been reported among workers at the German nickel refinery at Ludwigshafen. Again, there has been no abnormal rate for respiratory cancer among the Canadian nickel workers. It is not at all clear what kinds of exposure may be effective, or if nickel alone is responsible. Attempts have been made to explain the differences in attack rates among plants by indicting the arsenic content of the sulfuric acid used in certain of the locations. As Hueper (35) has pointed out, the absence of other evidence of exposure to arsenic tends to invalidate this explanation.

Arsenic. Though well known as an inciter of skin cancer in man, arsenic plays a weak if not doubtful role in the induction of lung cancer. The most suggestive evidence has been offered by Hill and Fanning (36), who reported that in one town in England where the principal industrial work is the manufacture of arsenic sheep-dip, the mortality rate for cancer among the workers was double that for the remaining population of the town. The difference in rates was due to increased cancer rates for skin and lung. On the other hand Snegireff and Lombard (37) in a study of a metallurgical industry in Massachusetts concluded that there were no significant differences in cancer mortality among workers engaged in the handling of arsenic trioxide. Hueper (35) interpreted their data

differently, and is of the opinion that prolonged inhalation of arsenic dusts and fumes resulted in an increased liability to cancer of the lung He further refers to his data from several counties in Montana in which copper ores of high arsenic content are mined and smelted. In these counties, lung cancer rates were 46, 48, and 145. These were compared with a rate of 5 2 for an agricultural county and of 10.9 for the United States as a whole The experience in Sweden is contrary to Hueper's (Smith (38)) In view of the years of study given this problem and the repeated failures to obtain definitive and concordant results, it is necessary to state that any role that arsenic may play in the production of lung cancer remains to be established

Other elements. Hueper (35) has written at length upon the possible relationship between exposure to metallic dusts and fumes and respiratory cancer. Ar [illegible] cadmium, [illegible] mercury, n[illegible] selenium, t[illegible] properties of most is either negative, inadequate, or merely conjectural Numerous studies over a period of many years have established the complete lack of carcinogenic action of aluminum. Our own observations on workers exposed to beryllium since 1939 (in excess of 55,000 man years) have failed to reveal a single case of bronchogenic carcinoma (39)

Pneumoconiosis Any direct carcinogenic effect of the pneumoconiosis-producing dusts is extremely doubtful Since the early report of Friedlander in 1885 (40), the possibility of lung cancer arising from the chronic inflammatory processes of a pneumoconiosis has been under investigation The lack of a significant role for processes of pulmonary tuberculosis and bronchiectasis appears to be established. Studies by Vorwald (41) and others agree in the conclusion that pneumoconiosis in general, and silicosis in particular, do not involve any predisposition of lung cancer

Pulmonary cancer arising in cases of asbestosis has been reported by Wyers (42). Gloyne (43) believes the association to be significant and causal, another, Wegelius (44), found no carcinoma in a study of asbestosis in Finland. Although lung cancer has been reported in autopsies of asbestotic lungs, there are at present too few cases and too little epidemiologic data to establish a significant relationship. Interpretations of associations are complicated by the differing compositions, associated materials, and conditions of exposure in the various parts of the world The data at present are suggestive but inference as to causal relationship is not warranted The medical literature up to 1955 contains references to approximately sixty cases of coexistence of asbestosis and lung cancer in the same patient.

The occurrence of lung cancer in a case of siderosis has been observed

occasionally and Vorwald and Karr (45) have reported three cases in hematite miners. Kennaway and Kennaway (46) have also observed a 2.25-fold increase in lung cancer rates among metal grinders. Only six cases were found and the authors do not consider a causal connection as established. Owing to differing working environments and multiple exposures and the like, no significance can now be assigned to the observation.

Organic compounds. There exists a considerable body of literature on the carcinogenicity of organic compounds for experimental animals. Study of the publications by Hartwell (47) reveals that approximately 25 per cent of organic compounds may be expected to induce a neoplastic response when applied in the proper dose and fashion to a suitable experimental animal. As applied to human lung cancer these results today are without direct significance.

There are however several industrial situations in which exposure to certain organic compounds is accompanied by high rates for lung cancer. Kuroda and Kawahata (48) found, in a six year period, 21 cases of lung cancer in a population of about 18,000 workers exposed to hot gases from tar and dusts at the illuminating gas generators in a Japanese steel mill. Hueper (35) reports similar rates for lung cancer among Canadian and United States tar workers. In the Japanese situation, the duration of exposure ranged from 9 to 23 years (average 16 years). Hydrocarbons, (e.g., 3,4-benzpyrene) have been isolated from tars and shown to be active carcinogens for the skin of mice—though not for some other species, including monkeys (9).

One case of lung cancer and six tumors of the paranasal sinuses or larynx were reported in 1952 (49). The seven cases occurred in a group of 71 employees engaged for more than five years in the manufacture of isopropanol. The nature of the process was such as to enable formation of condensed unsaturated rings. In addition, a high-boiling petroleum oil (Merrill oil) was added to the reaction. Specific carcinogenic hydrocarbons were not identified but fluorescence spectra were like those of polynuclear aromatic hydrocarbons.

GENERAL AIR POLLUTION

Only a very small proportion of our population is employed in industries where there are well-established and important lung cancer hazards as described above. However, virtually the entire population breathes air which is polluted in varying degrees by a wide variety of organic substances. Among these might be mentioned soot and fumes from coal and fuel oil, motor vehicle exhaust fumes, and dust from bituminous-surfaced roads and motor vehicle tires. Air pollution from these and

other sources has been steadily increasing, especially in urban and industrial areas. (See Fig 12 (50).) Whenever organic material is heated or is otherwise subjected to conditions leading to decomposition, carcinogenic compounds may be formed. This occurs most frequently during distillation, cracking, or combustion at high temperatures (usually above 800°F.). Under these conditions the organic material fragments and the

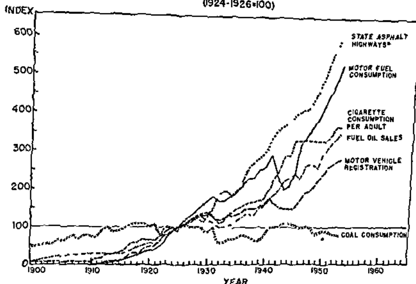


Fig 12

resulting carbon, hydrogen *et al*, will rearrange into a wide variety of stable configurations that will condense upon cooling. Among these may be carcinogens. For example, even a simple compound such as methane or acetylene will, upon proper conditions of heating, yield condensed *polycyclic hydrocarbons, including* 3,4-benzpyrene. Coal tar, retort tar, shale oil, catalytic cracked oil, and heavy fuel oils are examples of products of the processes noted above. Incomplete *combustion in coal-burning* devices, incinerators, oil burners and internal combustion engines has been shown to result in the emission of hydrocarbons that will induce tumors in mice (51–53) The significance of this as applied to lung cancer in man is undetermined The carcinogenic materials found in these effluents, *however, are chemically* identical with those found in coal tar, and they

arise from the same kinds of raw materials that have been treated under appropriate conditions. Since coal tar may be assumed to be capable of inducing lung cancer in man, it is a reasonable inference that the effluents in question may under certain circumstances also have that capability. Perhaps this inference can be tested when we have the necessary information on magnitudes of exposure, duration, and attack rates for lung cancer in the exposed groups, together with the necessary knowledge of the other experiences of the cohorts concerned.

Fifteen years ago exposure to radioactive materials was sharply localized and involved only a few thousand people in the United States. They were principally engaged in the mining and processing of radioactive ores, or were radiologists or makers of radio tubes, static eliminators, and luminous products. The development of fissionable matter for military purposes has increased the production of radioactive materials by many orders of magnitude, and has resulted in the manufacturing and dissemination of a large number of radioisotopes with increasing use in industry and research. It may be assumed that adequate safeguards and controls are in effect in those industries primarily concerned with the processing of fissionable matter and the preparation of radioactive isotopes. In other situations, however, there is no assurance of control, and responsible individuals in industries and laboratories using radioactive material should be alert to the dangers of inhalation of particulates.

Of considerably wider interest is the possibility of risk to the population by general air pollution with radioactive materials. It is obvious that factories processing thousands of tons of uranium will have an effluent, some of which will be rapidly dispersed in the atmosphere, and others in the waters, later to be concentrated by marine and plant life, and redispersed. Again, the testing of weapons will lead to high local concentration of radioactive fission products and unfissioned parent materials in the local atmosphere. Most will fall out quickly, and some will remain to be slowly mixed into the air envelope of the earth. Systematic analysis, however, reveals that any hazard to the general population is almost nonexistent insofar as past manufacturing and testing operations are concerned (54).

TOBACCO SMOKE

In 1928, Lombard and Doering (55) of the Massachusetts State Health Department made a study of the smoking habits of cancer patients as compared with the smoking habits of people free of this disease. They found a much higher percentage of heavy smokers among the cancer patients than among the controls. This was particularly true of patients with cancer of the buccal cavity. Lung cancer was a comparatively rare disease at that time and was not specifically mentioned in their re-

TABLE III

SUMMARY OF FINDINGS REPORTED BY 14 RETROSPECTIVE CLINICAL STUDIES ON THE ASSOCIATION OF SMOKING AND LUNG CANCER

Author	Country	Date	Number of Cases		Per Cent Who Were Nonsmokers Among Those		Per Cent Who Were Heavy Smokers Among Those		Relative Risk of Lung Cancer *	
			With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer	With Lung Cancer	Without Lung Cancer	All Smokers	Heavy Smokers
1	2	3	4	5	6	7	8	9	10	11
Muller	Ger	1939	86	86	3.5	16.3	50.0	10.5	5.4	22.2
Schairer & Schoniger	Ger	1943	93	270	3.2	15.9	31.2	9.3	5.7	16.7
Wassink	Neth	1948	136	100	5.0	19.0	55	19	4.5	11.0
Schrek et al	U S	1950	82	522	14.6	23.9	18.3	9.2	1.8	3.3
Mills & Porter	U S	1950	444	430	7.2	30.4	—	—	5.6	—
Wynder & Graham	U S	1950	605	780	1.3	14.6	51.2	19.1	13.0	30.1
McConnel et al	Eng	1952	93	186	5.4	6.5	38.5	23.8	1.2	1.9
Doll & Hill	Eng	1952	1357	1357	0.5	4.5	25.0	13.4	9.4	16.8
Wynder & Cornfield	U S	1953	63	133	4.1	20.6	67.6	29.3	6.1	11.6
Sadowsky et al	U S	1953	477	615	3.8	13.2	46.8	30.7	3.8	5.3
Koulumies	Fin	1953	728	300	0.6	18.0	65.8	25.0	36.4	79.0
Breslow et al	U S	1954	518	518	3.7	10.8	75.6	44.2	3.2	5.0
Levin	U S	1954	490	2365	8.0	26.9	52.7	22.7	4.2	7.8
Watson & Conte	U S	1954	265	287	1.9	9.7	73	57	5.5	6.5

* Relative risk of lung cancer is the ratio of the chances of a smoker developing lung cancer to those of a nonsmoker developing lung cancer For example, the entry on line one of col 10, 5 4, means that the risk of a smoker developing lung cancer is 5 4 times that of a nonsmoker

port The study was later repeated on a larger scale by the same department (56) The previous finding for cancer of the buccal cavity was confirmed, and in addition a much higher percentage of smokers was found among the lung cancer patients than among the controls. No less than 14 other independent studies of similar design have been made in this country and abroad The results, as summarized by Dorn (57–70), are shown in Table III (57) In every instance, the investigators found a much higher percentage of heavy smokers among lung cancer patients than among controls The magnitude of this difference varied considerably from study to study This was due in part at least to the fact that various authors have used quite different systems for classifying people according to their smoking habits For example, some considered only the amount of tobacco consumed per day while others considered the type of smoking and the number of years of smoking as well as the average daily amount Those who classified their subjects by type of smoking found a higher association between cigarette smoking and lung cancer than between pipe and cigar smoking and this disease Wynder and Graham (64) reported that the association was largely confined to epidermoid carcinoma of the lung and that there is little if any association between smoking and adenocarcinoma of the lung (which is the less common form of the disease).

Some criticisms have been made of the method used in these studies For this reason, three studies are now being conducted with a totally different design known as the prospective or follow-up method. The first findings from two of these studies were reported in June of 1954 Hammond and Horn (71) used volunteer workers of the American Cancer Society to obtain the smoking histories of a large number of white men between the ages of 50 and 70 The subjects were from 394 counties in nine states, namely, New Jersey, Pennsylvania, New York, Michigan, Illinois, Wisconsin, Minnesota, Iowa, and California Both urban and rural communities were included Of 187,766 men successfully traced, 4854 died within approximately twenty months from the time they were questioned According to the death certificates, 844 of the deaths were due to cancer of which 167 were attributed to primary cancer of the lung As shown on Table IV (71), the lung cancer death rate was nine to ten times as high among heavy cigarette smokers as among men who said that they had never smoked This difference is statistically significant, but the number of cases is not sufficient to make an exact estimate of the magnitude of the difference The lung cancer death rate for moderate cigarette smokers was about four times as high as among men who had never smoked There was no indication that pipe and cigar smoking is associated with the occurrence of lung cancer

Doll and Hill (72) have made a preliminary report on a similar study

TABLE IV

LUNG CANCER DEATH RATES BY TYPE OF SMOKING AND BY AMOUNT OF CIGARETTE SMOKING AT TIME OF QUESTIONING

Type of Smoking	Population	All Cases Reported as Primary Lung Cancer		Microscopically Proved Lung Cancer (Excluding Adenocarcinoma)	
		No of Deaths	Death Rate	No of Deaths	Death Rate
Never smoked or occasional only	44,091	12	27.2	4	9 1
Cigar and/or pipe smoking but never smoked cigarettes regularly	35,853	12	33 5	3	8 4
History of regular cigarette smoking	107,822	143	132.6	45	41 7
Total	187,766	167	88 9	52	27 7
Regular cigarette smoking, less than 1 pack a day at time of questioning	54,799	62	113 1	17	31 0
Regular cigarette smoking, 1 pack or more a day at time of questioning	25 497	61	239 2	24	94 1

of 24,389 British physicians (aged 35 and above) followed for 29 months. The findings were in essential agreement with those just described.

These numerous studies have established beyond doubt that cigarette smoking is associated with lung cancer and that the association increases with the amount of smoking Much has been written on other evidence related to the subject For example, the per capita consumption of cigarettes increased as the lung cancer death rate increased; a larger proportion of men than women are heavy cigarette smokers and lung cancer death rates are higher among men than among women, and cigarette smoke condensate has been used to produce cancer on the skin of mice (73). This supplementary information may mean very little since each piece of it is subject to various interpretations. Nevertheless, it is consistent with the hypothesis that cigarette smoking acts as one of the causative factors for the development of lung cancer. No evidence has been found to support any alternative hypothesis thus far proposed We are of the opinion that the high association between cigarette smoking and lung cancer reflects a causative relationship· this relationship may not be a simple one.

SUMMARY

1 The incidence of lung cancer has increased greatly during the last several deca [illegible]

2 There [illegible]

mates, nicke [illegible] tion of lung cancer in a few limited instances involving those engaged in specific industrial operations. A number of other substances have been suspected as causing lung cancer in industrial workers (e g , arsenic, asbestos, beryllium, and other agents capable of producing pneumoconiosis), but in our opinion the evidence for their causal role is insufficient.

3 Large segments of the population are exposed in varying degrees to air pollutants There is reason to suppose this is capable of causing lung cancer in man but at the present time epidemiologic evidence is insufficient to establish the fact

4 There is a high degree of association between cigarette smoking and the occurrence of lung cancer We are of the opinion that cigarette smoking acts as one of the causative factors for the development of lung cancer

5. The relative contribution of each of the foregoing to the present incidence of lung cancer is at this time conjectural

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4

Pathologic Aspects

Averill A. Liebow

Important information regarding the etiology of cancer of the lung has accrued with the years, and especially since an undeniable increase in the prevalence of the disease has stimulated interest However, there is as yet little knowledge of the pathogenesis of the various pulmonary neoplasms Before presenting a classification and description of these tumors, some general features deserve consideration.

CONSEQUENCES OF BRONCHIAL OBSTRUCTION

Most tumors of the lung begin in the large bronchi and soon obstruct them, or interfere with their function Partial or complete obstruction of bronchi may have any of several consequences· 1) emphysema· when inspired air is trapped by valving, 2) atelectasis when obstruction is complete, or when a valve mechanism permits egress, but not ingress, of air, 3) pneumonitis infection, as in any draining tract, characteristically follows obstruction The pneumonitis may be relatively silent In these instances it is largely interstitial, and the residual terminal air spaces become crowded with fat-laden phagocytes Grossly this tissue has an appearance that justifies the name "golden pneumonia" The exact mechanisms that underlie this so-called "obstructive pneumonitis" are unknown. On the contrary, rather than assuming this subtle form, the pneumonia may be of a necrotizing type Then it may have as sequels 4) bronchiectasis—a result not of uncomplicated obstruction, but of the organization of a necrotizing focal pneumonia that is ultimately converted into a series of scars, these scars, in contracting, pull upon more proximal relatively well-preserved bronchi This traction is probably the most important mechanism in the pathogenesis of bronchiectasis (1); 5) abscess results when necrosis in the lung is so extensive that a persistent cavity remains after organization is largely complete or reaches a stable state Most so-called abscesses associated with lung tumors are, however, not of this nature, but rather represent cavitations within tumor tissue, as will be discussed in relation to squamous cell carcinomas. Each of these sequels

of obstruction may be accompanied by appropriate, but sometimes confusing, symptoms and radiographic signs In roentgenograms, tumor may be difficult to distinguish from many of the sequels of obstruction

PATHOLOGY IN RELATION TO ANGIOGRAPHY

Recent angiographic studies have focused interest on changes in the intrathoracic vessels produced by tumors of the lung (2–4). Some of these are obvious, such as evidence of displacement, gross irregularity, or even obstruction of large intrathoracic veins with establishment of a collateral circulation Involvement of main pulmonary arteries may be similarly demonstrated Less widely understood, however, is the fact that when lung tissue is rendered immobile it receives less blood This is consequent to the very important influence of the bellows action of the thorax in pumping blood When this action is interrupted on one side, blood, and with it the angiographic contrast medium, is directed into the uninvolved side (5) In time the vessels on the diseased side tend to become smaller With reference to the intimate blood supply of the tumors, it has now been well established that primary tumors receive their blood from the systemic bronchial arterial system (6–8) Pulmonary arteries and veins, on the other hand, may actually be displaced by the tumor at its periphery (Fig 13). This might under favorable circumstances be demonstrable radiographically, as for example by catheterization and segmental angiography. This procedure will not, however, distinguish neoplasm from other lesions that also receive blood from the aorta rather than the pulmonary vessels, e g., tubercles, or bronchogenic cysts It may happen that pre-existing pulmonary arteries and veins become surrounded by the growing neoplasm although not obstructed, but this does not necessarily imply that they receive blood from these vessels. Perhaps this accounts for the diverse statements that have been made regarding the blood supply of pulmonary neoplasms On the contrary, as some have stated, it may be that metastatic tumors receive their blood supply from the pulmonary arteries (6) In our still limited experience this has not been confirmed and they have not differed from the primary lesions in their vascularization from the systemic bronchial arteries (Fig 14)

LYMPHATIC DRAINAGE OF THE LUNG AND OTHER ANATOMICAL FEATURES AFFECTING OPERABILITY

Not enough of the needed intensive study has been given to the lymphatic drainage of the lung in man Observations of Rouvière (9) and others suggest that the superior division of the left upper lobe drains



Fig 13 Blood supply of epidermoid carcinoma Vinylite cast A spherical mass has compressed the intermediate bronchus of the right lung into a thin ribbon and displaced the pulmonary arteries and veins, which are likewise flattened and distorted The true blood supply of the tumor is derived from greatly enlarged bronchial arteries (black), best seen in the region of the former capsule



Fig 14 Blood supply of pulmonary metastasis from hypernephroid carcinoma Vinylite cast Two small pulmonary arterial branches (labeled 1 and 2 in the photograph) join at an obtuse angle, since they have been displaced by a nodule of tumor A skeleton of bronchial arteries remains after the tumor tissue has been digested away The feeders of these vessels are seen extending from the hilum below and to the right along the bronchi leading to the involved parenchyma

nodes of the left side the left paratracheal group, the node of the ductus arteriosus, and the left anteromediastinal group including the node of the recurrent nerve. From other portions of the left lung, including the inferior division of the upper lobe, drainage is in part into the sub-

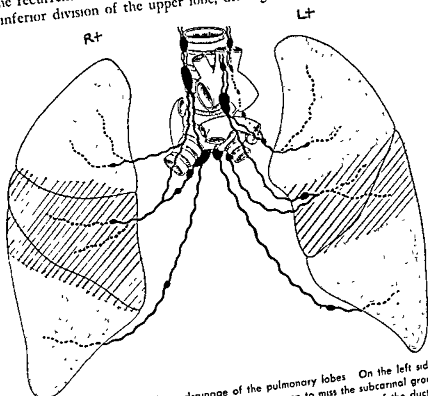


Fig 15 Diagram of lymphatic drainage of the pulmonary lobes On the left side, the drainage of only a portion of the upper lobe is seen to miss the subcarinal group of nodes but proceeds to the left paratracheal chain and to the node of the ductus arteriosus Most of the drainage of the right upper lobe is to the azygos node and to the paratracheal chain of that side The remainder of the pulmonary substance drains at least in part to the subcarinal group (From Ackerman, L. V., and del Regato, J A *Cancer, Diagnosis, Treatment and Prognosis.* St. Louis The C V. Mosby Co., 1947)

carinal group, thence it may extend toward the right side of the mediastinum On the right side drainage from the middle and lower lobes is into the subcarinal nodes, as well as other portions of the mediastinum, especially the right side Techniques have been described for removing these masses of nodes, including the subcarinal group, in a single block with the appropriate lung (10, 11). The value of this "radical pneumonectomy" in prolonging life remains to be determined It is obvious that the plane of dissection, even under the best circumstances, must pass within a millimeter of any tumor-bearing lymphatics or nodes (Fig. 15).

The mere demonstration of enlarged lymph nodes in the presence of bronchogenic carcinoma does not necessarily indicate the presence of metastatic tumor. These nodes may be the seat of lymphadenitis consequent to a pneumonitic process. Their radiographic demonstration by laminagraphic techniques or in esophagograms should therefore not be interpreted as an inevitable sign of a bad prognosis.

One feature of the anatomy of the lung that creates a problem in the surgical treatment of carcinoma is the intimate relation of certain bronchi to the pulmonary ligament and mediastinum. The dissection as ordinarily carried out then passes through a thin sheet of areolar tissue, hopefully separating the tumor, with the lung, from the structures left behind. When such bronchi are involved an intrapericardial approach to the vessels during pneumonectomy would seem to afford a better chance of cure.

ATYPICAL PROLIFERATION AND CARCINOMA *IN SITU*

Knowledge of the initial steps in the genesis of tumors of the lung is rudimentary. It may nevertheless be desirable to review some relevant although fragmentary observations, and to consider some possibilities for future investigation.

Atypical proliferation of tissues occurs in the course of healing of many types of pulmonary disease. Under this heading may be considered 1) squamous metaplasia, 2) Nonsquamous columnar or adenomatoid accumulations, 3) acinar proliferation and metaplasia of epithelium of distal respiratory passages, 4) hyperplasia of nonepithelial tissues. Moreover, the concept of carcinoma *in situ* requires separate discussion as it relates to the lung.

Squamous metaplasia is frequently observed in the organization of focal necrotizing pneumonia, of infarcts, in bronchiectatic sacs, healing abscesses, tuberculous cavities, and even in emphysema (Figs 16 and 17). This process was so striking in the postinfluenzal pneumonias as to stimulate the prediction that cancer of the lung would increase (12). There is little evidence, however, that any large proportion of pulmonary tumors has its basis in any of these lesions. Carcinoma of the lung has not increased disproportionately in Iceland, which suffered heavily from influenza in the great pandemic that followed World War I. Well-documented reports of carcinoma arising in bronchiectasis, such as that of Kornwaler and Reingold (13), are rare. There is some predominance of lung cancer in the upper lobes suggesting to some a relation to post-tuberculous scarring and metaplasia. Rarely, well-differentiated squamous cell carcinoma has demonstrably arisen in upper lobe cavities and invaded the structures of the chest wall and neck as a "Pancoast tumor."



Fig 16 Atypical proliferation in pulmonary emphysema In a thickened septum, amid the bullae, are irregular masses of squamous cells These suggest merely excessive proliferation with metaplasia, rather than carcinoma There is an invasive epidermoid carcinoma in the emphysematous upper lobe of the opposite (left) lung Compare with Figs 23 and 24



Fig 17 A high magnification of a field shown in Fig 16 Irregular but anaplastic squamous epithelium is present in masses of considerable size Intercellular bridges are well preserved

Approximately 10 per cent of the pulmonary carcinomas reviewed by Fried (14) had concomitant tuberculosis. Carcinoma of the lung arising in association with active tuberculosis has been described by Robbins and Silverman (15), among others. Carcinoma of the lung frequently arises in association with emphysema not related to obstruction by the tumor, and sometimes after long years of observation.

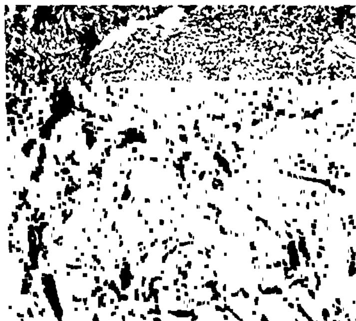


Fig 18 Proliferated epithelial cells of the mucous glands (?), within wall of bronchiectatic sac. These resemble the cells seen in certain bronchial adenomas (150×)

Minute accumulations of nonsquamous epithelial cells often occur in bronchiectasis or emphysema, in the lining epithelium of bronchioles or in the walls of small bronchi, and in a position suggesting an origin from the surface epithelium, or from mucous glands or their ducts (16–18). These cells are frequently columnar or ovoid, so as to suggest anaplastic carcinoma, and they may possess an arrangement resembling that of a minute bronchial adenoma (Figs 18 and 19). According to Prior (18) such changes are found particularly in older age groups, beyond 55 years, and are more common in women. This age and sex distribution alone makes it dubious that any large proportion of carcinoma has its basis in these cellular proliferations. They are furthermore so frequent in occurrence, that it seems probable that these proliferations are self-limited in

the vast majority of instances, and without malignant potentialities. The actual discovery of a metastasizing minute pulmonary carcinoma is distinctly rare (19).



Fig 19 Focal atypical epithelial proliferation involving remnant of mucous gland (?) in wall of bronchiectatic sac (250×)

Another type of atypical proliferation that occurs in fibrosing disease involves a remarkable hyperplasia of the epithelium of bronchioles, and either extends into more distal air spaces, or buds into newly formed granulation tissue, wherein, with the formation of scar tissue, it becomes imprisoned. This process is much more extensive and variegated than

the common and well-known epithelialization of alveoli (20, 21) The epithelial cells in this process vary in their deviation from the histotypical



Fig 20 Atypical proliferation difficult to distinguish from bronchiolar carcinoma Fibrosis with lymphocytic infiltration of the parenchyma Uppermost in the field is a bronchiole connected with the four largest of a series of ramifying spaces These are lined with various types of epithelium Most have a lining of tall columnar ciliated and mucus producing cells like those of the bronchiole itself Others are lined by cuboidal or flattened nonciliated cells. This process is interpreted as representing atypical regeneration with hyperplasia of the epithelium of bronchioles in the course of organizing pneumonitis

They are often of tall columnar type, some are ciliated, and some are tall mucus-producing cells of unusual appearance, but quite like those that form the predominant element in the better differentiated forms of metastasizing bronchiolar carcinoma (Figs 20 and 21).

Thus it appears that there is some evidence to suggest that cancer of the lung may begin as atypical proliferation, but that this is the initiating lesion in any large proportion of bronchogenic carcinomas requires further



Fig 21 Same lung as illustrated in Fig 20 Stratified squamous as well as ciliated epithelium lining other air spaces

proof Of particular interest would be evidence that some specific agent, for example a virus, as is considered probable for the infectious disease of sheep known as *jaagsiekte* (22, 23), is the etiologic factor.

"Carcinoma *in situ*," or "precancerous metaplasia," has been demonstrated or postulated for many types of neoplasms A fundamental study of this subject was made as early as 1935 by Lindberg (24), who demonstrated changes of this type not only in the mucous membrane, adjacent

to bronchogenic tumors (Fig 22), but also in remote bronchi, and in some instances, even of the other lung. In Lindberg's experience definite invasion was apparent in a few cases, and in two instances small carcinomas existed in addition to the major tumor. There has been confirmation from other sources (25). Carcinoma *in situ* has also been found in resected lungs following the discovery of atypical cells in the sputum, in the absence of other histologic evidence of carcinoma (26, 27).



Fig 22 Carcinoma *in situ* Highly atypical epithelium in the lamina propria of a bronchus that in the near vicinity is the origin of a truly invasive epidermoid carcinoma

Considerable atypical proliferation of nonepithelial tissue has also been noted In some organizing processes, muscle becomes so abundant that the diagnosis of leiomyoma has sometimes been employed, probably mistakenly, since lesser degrees of this process are exceedingly frequent (28) Fibrous connective tissue can also become hyperplastic to such an extent as to suggest tumor formation, and this process as well usually appears to be self-limited Occasionally, collagenized material is left behind as hyperplastic muscle tissue becomes hyalinized This change may proceed within the parenchyma, or, in polypoid fashion, in the lumen of a bronchus

CLASSIFICATION

A study of many malignant tumors of the lung has demonstrated that their natural history depends in some measure upon their microscopic structure Since different parts of the same bronchogenic carcinoma

may vary microscopically, the classification is made according to the predominant cell type and presumed histogenesis, but the term "mixed" is applied when this is not possible.

I Primary malignant epithelial tumors
  A. Bronchogenic
    1. Epidermoid carcinoma
    2 Anaplastic carcinoma
    3. Adenocarcinoma
    4. Mixed type
  B. Bronchiolar carcinoma ("pulmonary adenomatosis," "alveolar cell carcinoma," etc)
  [C. "Bronchial adenoma"]
    1 Carcinoid type
    2. Cylindromatous or adenocystic type
    3 Others
II. Sarcoma of the lung, central or peripheral
  A. Undifferentiated spindle-celled sarcoma
  B Differentiated sarcoma
  C Primary lymphosarcoma
III. Mixed epithelial and sarcomatous tumors (carcinosarcoma, mixed tumors)
IV Neoplasms of the reticuloendothelial system involving the lung as part of a generalized process
V Metastatic tumors of the lung

Although this classification is not universally accepted, it has the merit of simplicity. As simple a classification as possible should be retained until specific subgroups can be delineated Opinions differ as to whether the "bronchial adenomas" should be classified with the other tumors in this group They are therefore bracketed and the problem will be discussed briefly

Epidermoid carcinoma Epidermoid carcinoma comprises between 45 and 60 per cent of all bronchogenic tumors, depending upon what is included under this heading.

It seems probable that most epidermoid tumors have their origin in the surface epithelium of the bronchi Evidence for this is the frequent existence of "carcinoma *in situ*," not only adjacent to the invasive tumors, but at times in remote zones of mucosa, as has been described above It seems probable, however, that carcinoma rarely arises in ordinary metaplastic epithelium, since metaplasia occurs so frequently, and carcinoma is so relatively rare (Figs 23 and 24)

Histologically, there is evidence of keratinization in the most mature



Fig 23 A large squamous cell carcinoma arising in the upper lobe of a lung known to have been emphysematous for many years The upper lobe bronchus is involved, but the tumor extends far to the center of the lobe, where it probably had its origin The right upper lobe is the seat of the metaplastic process illustrated in Figs 16 and 17



Fig 24 Microscopic section of the fairly undifferentiated epidermoid tumor shown in Fig 23

forms, that may be called squamous cell carcinoma. Epithelial pearls and intercellular bridges may be demonstrable. There are, however, many tumors much less differentiated than this, but still easily identifiable as epidermoid carcinoma, just as there are in the skin. The line of distinction drawn between some of these tumors and those classified as "anaplastic carcinoma," is arbitrary. This explains differences in statements regarding the natural history of these tumors (29, 7, 30). Patton and his co-workers (31) have used the term "large cell carcinoma" for a group of tumors not obviously squamous, and composed chiefly of rather large cells. These make up 40.2 per cent of all bronchogenic carcinomas in their series In their discussion they state, "We have taken the surprising survival of some of these patients to mean that a goodly proportion of the lesions actually must be squamous-cell carcinoma which are of such high grade that they cannot be diagnosed and yet carry over some of the better prognosis to be expected of the squamous-cell type of bronchogenic

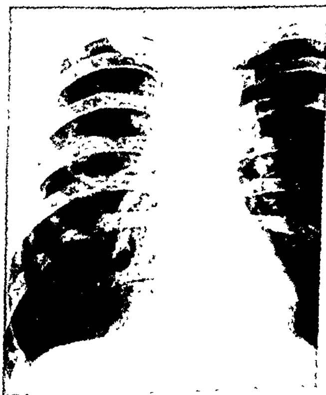


Fig. 25. Epidermoid carcinoma A thin-walled cavity is seen in the midportion of the right lung Lateral views demonstrated this cavity to be in the superior segment of the lower lobe Compare with Fig 26.

carcinoma" In the present classification most of these tumors have been included with the epidermoid group

The designation "pleomorphic cell carcinoma" of the lung has been applied by Smetana, Iverson, and Swan (32) to a small group of tumors encountered largely among older patients They consider the growth of these tumors to be more slow, as evidenced by the longer duration of symptoms, generally four to eight years These tumors were said to be situated more peripherally than most bronchogenic carcinomas, and tended to become markedly excavated (Figs 25 and 26) Histologically, they were described as consisting of very bizarre elements, with many giant cells, the nuclei of which are rich in chromatin (Fig 27). The stroma was reported to be poor in reticulum fibers Since cells of this spindle type are found in many tumors otherwise clearly epidermoid, and since they are in fact at times predominant, it would seem that these too should be classified with the epidermoid tumors A careful search usually is rewarded with the discovery of some epidermoid tissue in "pleomorphic cell carcinoma" (Figs 28 and 29)

Grossly epidermoid carcinoma appears most commonly as a pear-shaped mass (Fig 30) of translucent pink tissue flecked with the black of anthracotic material and with the chalky yellow of foci of necrosis It surrounds in bulk a lobar or segmental bronchus, and frequently one or several orders of branches beyond Since the pulmonary tissue is likely to have suffered alteration consequent to obstruction of the bronchus, it is usually not possible to state how much of the roentgen shadow is actually tumor Since the narrower end of the "pear" is closer to the hilum, it appears probable that the actual point of origin of most tumors is beyond the bronchus most proximally involved A stalk of tumor may actually present itself within the lumen of the bronchus at the hilar end of the lesion This can sometimes be demonstrated radiographically, particularly by the sectioning techniques, as an abrupt interruption of the bronchus Proximal extension may also be demonstrated microscopically within the wall of the bronchus deep to the surface, but usually not more than one or two cm. proximally of the gross visible lesion (33) The tumor may, however, reappear on the surface proximal to the main mass, *with an irregular ring of uninvolved mucous membrane between.*

Rather than expanding into tissue surrounding the bronchus of origin, epidermoid tumors may remain more or less confined to the lamina propria, with the replacement of the normal epithelium by irregular masses of tumor cells, and the lumen of the bronchus may be minimally narrowed or not at all. Bronchial drainage may nevertheless be disturbed by a relatively small lesion of this type, the bronchoscopic appearance of which often suggests granulation tissue rather than neoplasm Such a tumor, no less than a truly obstructing mass, may have behind it a large zone



Fig 26 Epidermoid carcinoma Medial aspect of the lung shown in Fig 25 The cavity has a rather smooth lining with only a few rounded irregularities This appearance might suggest abscess, but is belied by the extensive anthracotic pigmentation that is more indicative of tumor The posterior wall is thicker than would be suggested by the roentgenographic appearance as seen in Fig 25

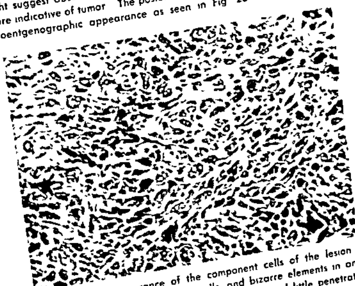


Fig 27 Pleomorphic appearance of the component cells of the lesion shown in Fig 26 There are many spindle-shaped cells, and bizarre elements in an arrangement suggesting sarcoma The reticulum stain demonstrated little penetration of the argyrophilic fibers among the cells



Fig 28 Another field Spindle shaped cells are gathered into small groups, separated by abundant stroma This appearance is now more suggestive of certain epidermoid tumors



Fig 29 Another field from the lung illustrated in Figs 25 to 28. The grouping and appearance of the cells is clearly that of epidermoid carcinoma

of pneumonitis or its complication, such as bronchiectasis or abscess. Thus the size of the roentgen shadow is not necessarily a guide to the size of the actual neoplasm (Figs. 31 and 32). There have been unfortunate instances of delay in surgical treatment, occasioned by attempts to



Fig 30 An epidermoid carcinoma that projects as a polypoid mass into the "intermediate bronchus" common to the right middle and lower lobes There is fibrosis with shrinkage of the right middle lobe; the greater bulk of the tumor within the substance of the lower lobe indicates an origin more peripherally than the intermediate bronchus where the tumor was presented to the bronchoscope There is scattered anthracotic pigment, as well as focal necrosis, in the tumor

"shrink" with radiation therapy such a presumed tumor mass, which in reality represents consolidated but not carcinomatous tissue.

Occasionally a bizarre distribution of the lesion may be encountered radiographically, when the tumor invades a somewhat remote bronchus by penetrating from a node Thus there may be an irregular mass in one lobe, and a wedge-shaped zone of atelectasis or pneumonitis in another (Figs. 33–35).



Fig 31 Epidermoid carcinoma Shadow in the lower lung field interpreted as largely representing tumor Irradiation was carried out over a seven-month period, and the right lung was then resected (Compare with Fig 32)



Fig 32 Epidermoid carcinoma The actual tumor is very small and presents as a rough elevation of the surface of the bronchus It has narrowed the intermediate bronchus, and extends for a short distance into the middle and right lower lobe branches The tumor invades the node between these major branches The middle lobe bronchus extends to the right and above the node, and a narrowed lower lobe bronchus extends downward and to the left



Fig 33 Epidermoid carcinoma Rounded density in the right upper lobe A wedge-shaped zone representing atelectasis of the middle lobe with its base upon the hilum, extends part way into the lung field (Compare with Figs 34 and 35)



Fig 32 Epidermoid carcinoma The actual tumor is very small and presents as a rough elevation of the surface of the bronchus It has narrowed the intermediate bronchus, and extends for a short distance into the middle and right lower lobe branches The tumor invades the node between these major branches. The middle lobe bronchus extends to the right and above the node, and a narrowed lower lobe bronchus extends downward and to the left



Fig 33 Epidermoid carcinoma Rounded density in the right upper lobe A wedge-shaped zone representing atelectasis of the middle lobe with its base upon the hilum, extends part way into the lung field (Compare with Figs 34 and 35)

The epidermoid tumors are not confined to the major bronchi, and may present themselves as peripheral or even subpleural masses Such lesions tend to be relatively silent clinically until the pleura or body wall is invaded. A lung tumor that invades the body wall is more likely to



Fig 34 Epidermoid carcinoma The posterior position of the mass shown in Fig 33 is demonstrated, as well as the densely atelectatic middle lobe. This film is printed in reverse of the usual, for comparison with Fig 35

be a very well-differentiated squamous cell tumor than any other type of bronchogenic carcinoma Perhaps the reason for this is that adenocarcinoma, although more commonly peripheral in location, is likely to have metastasized and to have manifested itself in consequence of this before the body wall has become invaded When such a well-differentiated epidermoid tumor takes origin in the periphery of the upper parts of the lung, as for example in a tuberculous cavity, invasion of structures at the upper thoracic inlet may take place. This produces a characteristic

group of symptoms described by Pancoast, the superior sulcus or Pancoast syndrome (34, 35), in which there is usually destruction of the sympathetic ganglions with Horner's syndrome, loss of power in the arm, pain, edema of the upper extremity, and evidence of destruction of ribs or vertebrae A similar syndrome, of course, may result from any destructive



Fig 35 Epidermoid carcinoma The primary tumor is seen to occupy almost the entire posterior segment of the right upper lobe Tumor from a lymph node (arrow) has invaded the middle lobe bronchus, producing a high degree of stenosis The entire middle lobe is atelectatic and the seat of "obstructive penumonitis" Its pale appearance contrasts with the darker color of the overexpanded anterior segment that lies above it Below the origin of anterior segmental bronchus is another mass of nodes that has not significantly compressed it

lesion in this portion of the body, but statistically it is predominantly the consequence of well-differentiated squamous cell carcinoma

Necrosis commonly occurs in epidermoid tumors, especially in the more differentiated squamous forms, and frequently there is discharge of necrotic material with cavitation Cavities reach a size in excess of 4 cm in diameter in approximately 20 per cent of epidermoid tumors by the time they are seen at necropsy. Occasionally the cavitation far exceeds this magnitude (Figs 36, 37) Thus carcinoma may have a roentgenographic appearance suggesting abscess. Such lesions, however, rarely have a history or symptomatology appropriate to true abscess, and

they may occur anywhere in the lung. Their walls tend to be relatively thick and are sometimes demonstrably irregular. The differential diagnosis can be difficult when the lining is apparently smooth, and when the



Fig. 36 Epidermoid carcinoma The region of the superior segment of the left upper lobe is occupied by an obviously cavitated mass In the upper third of this cavity there is a roughly triangular density with its base upon the hilum, and another, shelflike protrusion is seen below it (Compare with Fig 37)

lesion is located in a part of the lung where abscess is common, *i.e.*, in the "path of aspiration"—the posterior segments of the upper lobe, and the superior and basal segments of the lower lobe (Figs 25, 26). Nor do all pyogenic abscesses have a typical history and symptomatology. Expert cytologic examination of sputum or bronchial secretions is important in the differential diagnosis, when bronchoscopic or other techniques have failed (1). It is remarkable that even the most thin-walled of these

cavitations associated with bronchogenic carcinoma are usually lined by an uninterrupted layer of tumor cells

It is of course possible that a cavitative lesion may consist in part of necrotic tumor, and in part of necrotic lung This is sometimes demon-



Fig 37 Epidermoid carcinoma The lateral half of the lung shown in Fig 36 viewed from the medial side after resection Not only the superior segmental bronchus, but also the posterior basal bronchus is in communication with the huge cavitated mass The triangular density noted in Fig 36 is seen to be tumor tissue lipping the superior segmental bronchus as it enters the cavity The shelflike protrusion below is a similar mass above the communication of the posterior basal bronchus Posteriorly (at the left of the photograph) there is dense white tissue representing pleura and endothoracic fascia invaded by the well differentiated squamous tumor

strably the consequence of invasion of blood vessels by the tumor with infarction of the lung Under these circumstances bacterial infection often is superimposed and becomes a complicating and clinically confusing factor True abscess behind an obstructing carcinoma of the lung is relatively uncommon When the lesion is in the apical or posterior segments of the lung, cavitative tuberculosis may be closely simulated

From recent observations on patients who have been "followed" after a questionable roentgen shadow has been demonstrated, and from the

valuable review by Rigler and his co-workers (36) of *early survey* films of patients who later proved to have neoplasms, it seems probable that some bronchogenic carcinomas, especially of the epidermoid type, may grow more slowly and have a much longer existence before identi-



Fig 38 Epidermoid carcinoma Rounded mass visualized in November, 1950, when the patient, a hospital employee, was 69 years old. This is a routine film in an essentially asymptomatic individual

fying symptoms appear than has been realized in the past (Figs 38–41). Their course, once the diagnosis is made, is a very variable one.

Epidermoid carcinoma may reach an enormous bulk by continuous growth when situated in the center of a lobe, without invasion of surrounding structures or extrathoracic metastases, and even without alarming symptoms of pulmonary disease (Fig. 41). Growth along bronchial walls has already been discussed.

More so than malignant bronchogenic tumors of other types, the epidermoid carcinomas, and especially those to which the designation squamous is applicable, seem for a long time to remain confined to the paren-

chyma and to nodes immediately adjacent to the bronchus of origin. In fact, such nodes seem at first to be engulfed by the primary mass, rather than entered by lymphatic permeation True lymphatic extension ultimately occurs

Involvement of lymph nodes has a definite prognostic significance as



Fig 39 Same patient as in Fig 38 Film of January, 1952 Progression in size of the nodule is demonstrated

indicated by the observations of Carlisle, McDonald, and Harrington (29) 63 2 per cent of patients survived five years after resection when the regional lymph nodes showed no evidence of carcinoma in routine microscopic examination, whereas in those whose nodes contained tumor, the five-year survival rate was only 25 per cent

With the growth of the tumor, pulmonary arteries and veins may be invaded, rather than merely displaced Invasion of arteries usually does relatively little harm, but in some instances there may be infarction of the lung beyond. Invasion of pulmonary veins opens the entire systemic circulation to metastasis. Expanded collateral bronchial venous channels

connect with the azygos, and thus with the spinovertebral veins—a pathway to the bony axis and central nervous system (37, 38).

Although hematogenous metastases tend to appear *relatively late* in epidermoid carcinoma, they nevertheless pursue the same general pathways as *other* types of bronchogenic carcinoma (14, 39). Most com-

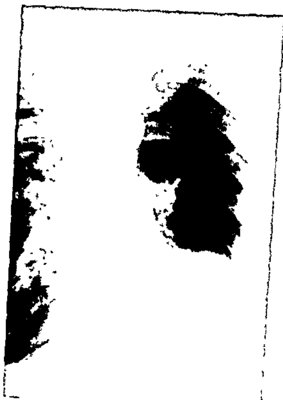


Fig 40 Same patient Film of May, 1954, at age of 73 The mass has now grown much larger At this time the patient complained only of mild cough productive of two to three tablespoons of nonsanguinous sputum

monly involved at the time of necropsy besides the regional lymph nodes, are the liver, bones, adrenals, and kidneys. Less frequent is metastasis to the brain, although evidence of neurological disturbance may be the first sign of the disease. The pericardium and heart are occasionally involved, chiefly by direct extension, and the pancreas may be the seat of lymphogenous metastasis.

Favorable effects of radiation therapy in prolonging life and in increasing the comfort of the patient and rendering certain cases operable, have been observed clinically with epidermoid carcinoma It has yet to

be demonstrated that any significant number of cures has been obtained with radiation therapy alone. Anatomically massive fibrosis of the region of the tumor has been observed, with only a small residuum of altered cells (Figs 42–45) With further advances in radiation treatment, it will be of interest to investigate more of these specimens as they are removed surgically



Fig 41, Abundantly keratinized squamous carcinoma with cavitation The mass occupies the subsuperior and posterior basal segments

Anaplastic carcinoma Approximately 30 per cent of the bronchogenic tumors fall into the anaplastic group according to the present classification

Various opinions have been expressed regarding the histogenesis of anaplastic carcinoma According to one of these, they arise from and retain the characteristics of "reserve cells" of the mucous membrane. These are small dark cells situated between the basement membrane and the differentiated epithelial cells of the surface into which they are ordinarily transformed Others have considered the anaplastic carcinoma is to be undifferentiated adenocarcinoma If this is true, it is strange that adenocarcinoma occurs six times more frequently in women than does

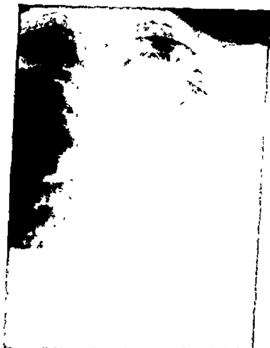


Fig 42 Epidermoid carcinoma of the lung Roentgenogram of chest before beginning of x-ray treatment A polypoid mass of tumor tissue was visible at this time in the left main bronchus near the carina Atelectasis and massive infiltrations in both lobes of the left lung Trachea deviated markedly to the left.

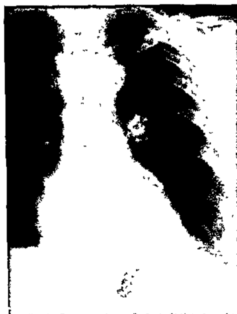


Fig 43 Same patient as in Fig 42 after x ray therapy The infiltrations have cleared except from a small patch near the hilum in the middle lung field The trachea has now returned to its midline position The patient was at this time considered operable and pneumonectomy was performed



Fig 44. Lung shown in Figs 42 and 43 after resection The anterior bronchus of the left upper lobe is occupied by a gray-tan, apparently solid mass. There is no projection of tumor beyond the wall of the bronchus There is an irregular zone of "golden pneumonia" in the parenchyma beyond



Fig 45 Microscopic section of the lung shown in Figs 42—44 At the level of section, the cartilage of the anterior segmental bronchus has been largely destroyed The wall consists of dense fibrous connective tissue infiltrated chiefly by lymphocytes and plasma cells Necrotic material occupies a portion of the lumen There is a lining of squamous cells, generally in a single layer In one region there is a large mass of squamous epithelium sufficiently anaplastic to be considered residual or regenerating carcinoma, rather than heaped-up metaplastic epithelium

anaplastic carcinoma. Moreover, the latter tends to be central while two-thirds of adenocarcinomas occur in a segmental bronchus or subsegmental bronchus. It must be admitted that metastases from some anaplastic carcinomas may possess the structure of well-differentiated adenocarcinoma (Figs. 46, 47). More commonly, however, islands of well-differentiated squamous cells may be observed within the most



Fig 46 Anaplastic carcinoma Primary lesion in the lung Spindle-shaped and ovoid cells arranged in irregular masses and cords (Approximately 100×)

anaplastic tumors (Figs. 48, 49), or the metastases may be anaplastic and the primary epidermoid, or the reverse. These observations support the concept that anaplastic tumors are composed of primitive cells capable of transformation into either glandular or epidermoid neoplasms, most commonly the latter. Curiously, in transplantation experiments, the most highly undifferentiated form, the "oat cell" tumors, maintain their original histologic structure without differentiating into squamous tumors (40). Thus there is some reservation in immediately accepting all of these tumors simply as undifferentiated epidermoid carcinoma.

Among anaplastic tumors belong the "oat cell" carcinomas, called "reserve cell" by some (41). These consist of masses of cells that bear some resemblance to lymphocytes. In fact such tumors were consid-



Fig 47 Metastasis in adrenal from the tumor illustrated in Fig 46 Here the tumor has the appearance of a well-differentiated papillary adenocarcinoma with psammoma bodies (Approximately 100×)

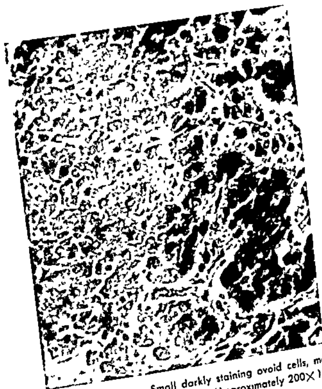


Fig 48 Anaplastic carcinoma Small darkly staining ovoid cells, many in mitosis Arrangement similar to that shown in Fig 46 (Approximately 200X)



Fig 49 Another field from the tumor illustrated in Fig 48 There is a group of squamous cells with distinct intercellular bridges, within an island of anaplastic carcinoma. (Approximately 200×)

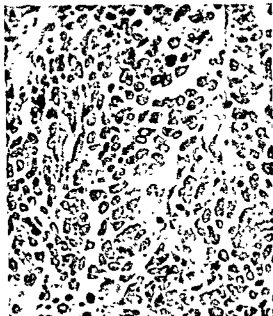


Fig 51 Anaplastic carcinoma Another case Cells are more variable, more loosely arranged, more elongated, and with more abundant cytoplasm than those shown in Fig 50 (Approximately 200×)



Fig 52 Anaplastic carcinoma The cells are smaller and somewhat more variable in outline than those illustrated in Figs 50 and 51 They are arranged in groupings suggesting those often seen in epidermoid carcinoma (200×)

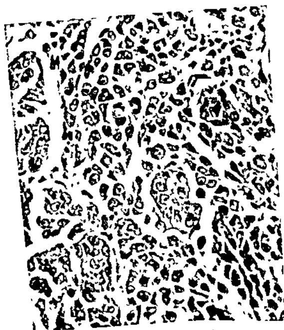


Fig 53 Anoplastic carcinoma, with cells transitional to the epidermoid type (Approximately 200×)

predominate in the stem bronchi of each lung, and rarely occur beyond the lobar bronchi. True peripheral tumors of anaplastic type are distinctly uncommon Typically the tissue is pale and translucent. Necrosis tends to be minimal and is rarely sufficient to result in gross cavitation



Fig 54 Anaplastic carcinoma Right hilar mass continuous with a mediastinal mass that extends upward toward the neck Notching typical of carcinoma is visible on the lateral aspect Collapse of the right lower lobe has not occurred, but there is a recticular appearance in the perivascular regions suggestive of lymphogenous spread. Compare with Fig 55

The nodes are massively involved even when the primary lesion is small, and this may occur at a time when the main bronchus has not as ye[t] become obstructed. Involved nodes and lymphatics extend in grea[t] collar-like masses proximally along the bronchial wall, beneath the carin[a] and into the main mediastinal chains Consequently they often prese[nt] as hilar masses in which the shadows of the parenchymal mass and lymp[h] nodes are continuous with each other and with that of the hilar stru[c]tures (Figs 54, 55). Invasion of lymphatics also progresses periphera[lly] about the bronchovascular rays and in the septa of the lung (Fig. 5



Fig 55 Anaplastic carcinoma involving the right stem bronchus, as seen from the posterior aspect Lung of patient shown in Fig 54 at necropsy Many lymph nodes are involved, including the subcarinal, paratracheal, and the node of the ductus arteriosus The last mentioned is seen below the transected aorta The shape of the tumor conforms to that observed in the roentgenogram The characteristic notching is visible The bronchus has become markedly narrowed, but is not completely obstructed The generally well-aerated substance of the right lower lobe is seen beneath the tumor, but there are streaks and minute nodules of gray tissue representing tumor within lymphatics

Consequently the "sunburst" appearance typical of lymphogenous spread may be evident in the roentgenograms in late cases. Although evidences of bronchial obstruction may often occur late in the disease, they are usually massive

Once symptoms exist and the diagnosis is made, the progress of the lesion is usually a rapid one and survival beyond the space of a year is uncommon. Although spread is predominantly via the lymphatic chan-

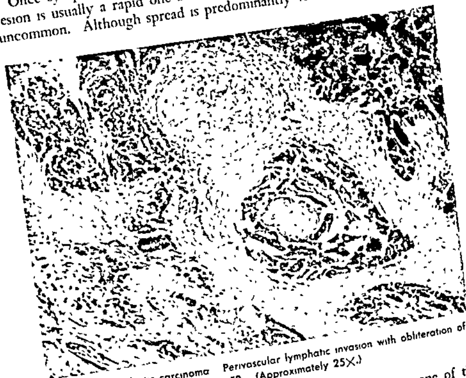


Fig 56 Anaplastic carcinoma Perivascular lymphatic invasion with obliteration of vessels Same instance as in Fig 52 (Approximately 25×.)

nels, hematogenous metastases are not uncommon In fact one of the latter, for example a pathologic fracture of a long bone, may be the first evidence of an anaplastic carcinoma

Adenocarcinoma Approximately 15 per cent of pulmonary cancers are adenocarcinomas. It is possible that many, perhaps most, adenocarcinomas of the lung take origin in the surface epithelium. Papillary adenocarcinoma that grows into the lumen of a bronchus, is almost certainly of this origin There are some tumors of this sort that have so regular an arrangement that their malignancy is in doubt In some instances there is evidence highly suggestive of an origin in the mucous glands, since atypical glands transitional to those of the tumor are demonstrable (Figs 57, 58). Certain adenocarcinomas have anaplastic portions quite similar to those of the malignant salivary gland tumors, such as may arise

for example in the parotid It would appear most unlikely that many of the malignant lung tumors take origin in the so-called bronchial adenomas They lack the lengthy history of symptoms of pulmonary disease that characteristically accompanies the bronchial adenoma. Discussion



Fig 57 Adenocarcinoma A bulky mucus-producing tumor that expands from the depths of the wall into the lumen of a large bronchus At the base of the tumor there are transitions from normal mucous glands to neoplastic tissue Compare with Fig 58 (Approximately 25×)

relevant to the "cylindromatous" variety of these tumors is presented below Furthermore, metastasizing tumors, both of the cylindromatous and carcinoid varieties, seem to retain their original structure. The problem of distinguishing between bronchogenic adenocarcinomas and bronchiolar carcinomas will be discussed.

Mucus can be demonstrated in the cells of most (approximately 85 per cent) adenocarcinomas of the lung (42) It may be present in a few cells only, and if the tumor consists predominantly of solid masses of large cells, with relatively few acinar structures, it offers an especially

valuable distinguishing feature. In some instances acinar structures may be much more prominent in metastases than in the primary lesion. An interesting papillary variant exists, that presents all gradations from regular ingrowths into the bronchi that may be considered benign, to rather wild-looking growths with highly irregular epithelium, numerous



Fig. 58 Higher magnification (approximately 100X) Transitional forms from normal mucous glands to acini lined by variable, deeply staining basophilic cells Numerous plasma cells infiltrate among the glands

mitoses, necrosis, and hemorrhage. As with papillary tumors in other sites, concentric lamellated masses of calcific material may occur in these tumors, the so-called psammoma bodies Malignant mucoepidermoid tumors similar to those of salivary glands (43) may present as bulky intrabronchial growths The natural history of lesions of these types as compared with the more common adenocarcinomatous tumors, remains to be determined.

Although most of the adenocarcinomas involve the segmental bronchi and their immediate branches, relatively more occur peripherally than

is the case with other histological types (7, 44). These tumors ordinarily have a pearly gray translucent appearance, and the cut surface is finely flecked with black anthracotic pigment Grossly visible foci of necrosis are generally small, and cavitation, although it may occur, is relatively



Fig 59 Adenocarcinoma Routine chest film in a 30 year-old x-ray technician, asymptomatic at this time Film of March 1952



Fig 60 Same patient as in Fig 59, ten months later Film of January, 1953 The mass had increased enormously in bulk indicating a rate of growth much greater than that of the well-differentiated squamous cell carcinoma in Figs 38–41 Compare with Fig 61

uncommon In particular, cavities in excess of 2 cm are rarely encountered A glairy cut surface, suggestive of a large content of mucus, is sometimes observed. This is only rarely encountered in the gross. Despite the peripheral position of adenocarcinoma, the chest wall is not commonly involved before the tumor has otherwise manifested itself

Data regarding the rate of growth of adenocarcinoma before it reaches a clinical level is difficult to obtain, but it would seem from serial films of "coin lesions" that had been unwisely "watched," that growth is rapid

as contrasted with that of squamous cell tumors (Figs 59–61). Hematogenous metastases tend to occur early and widely from otherwise silent pulmonary lesions. Their often peripheral position accounts for their insidious growth within the lung. Lymphatic pathways are also not neglected in metastasis.



Fig 61 Adenocarcinoma Same patient as in Figs 59 and 60 The peripherally situated soft bulky mass lies within the anterior basal segment of the right lower lobe There are small foci of hemorrhage, but without massive cavitation Lymph nodes containing metastatic tumor are shown within the hilum above and to the right

Bronchiolar carcinoma ("alveolar cell carcinoma," "pulmonary adenomatosis"). Recent observations (45–50), and especially the extensive summary of Storey, Knudtson, and Lawrence (*51*), have expanded the knowledge of the natural history of peripheral acinar tumors, variously called bronchiolar carcinoma, alveolar cell tumor, or pulmonary adenomatosis. These are epithelial neoplasms of various degrees of differentiation that seem so peripheral as not to be associated with any major bronchus

The tumor cells appear to be supported in large part upon the walls of alveoli This has suggested to some that such tumors may be of "alveolar cell" origin. This fact does not necessarily indicate the histogenesis.

since alveoli may serve as a support for metastatic tumors. When the sections are viewed *with the low power it is possible in most instances* to demonstrate that the tumor is centered about a bronchiole, in such a manner as to suggest that the bronchiole is the origin of the tumor; that is, it is difficult to conceive of tumor arising in alveoli to "creep up" into the bronchiole, to replace in part its mucous membrane, and to assume

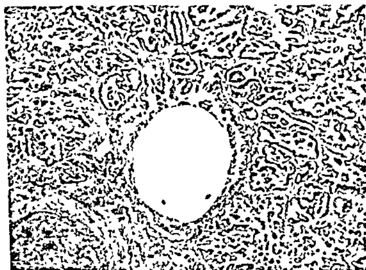


Fig 62 A bronchiole, the lining membrane of which has been replaced by atypical epithelium in papillary arrangement Near the upper margin the wall is interrupted and the edge of the epithelial lining continues into the surrounding spaces that are lined by similar cells The walls of these spaces are much thicker than those of normal alveoli

a distribution within the parenchyma with the bronchiole as the center (52, 53) (Fig 62) It is quite possible, however, that this appearance is produced by bronchogenic spread of neoplasm Metastatic neoplasms may have this appearance and even the lining membranes of large bronchi may be replaced by tumors originating elsewhere (Figs 63, 64) The possibility of successfully transmitting experimental tumors by intratracheal inoculation has been demonstrated (54) In man a "cancerous pneumonia" with intact alveoli distal to a bronchogenic carcinoma is occasionally encountered, and is further evidence of an aspirative mechanism in the spread of tumor (Fig 65) Consequently a focal intra- and peribronchiolar distribution is not necessarily conclusive as evidence of bronchiolar origin. Some other bits of evidence, however, suggest that



Fig 63 Metastatic carcinoma primary in colon, lining a bronchiole and extending into surrounding air spaces in a manner suggesting bronchiolar carcinoma



Fig 64 Metastatic carcinoma primary in colon The epithelium of even a stem bronchus has been replaced by metastatic cells

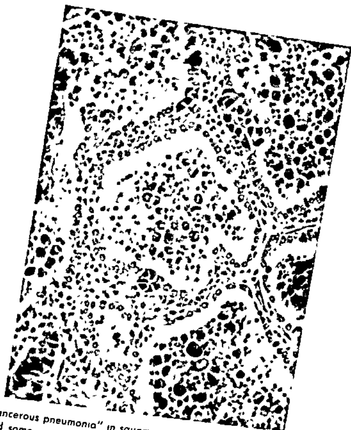


Fig 65 "Cancerous pneumonia" in squamous cell carcinoma The distal air spaces are filled and some are partly lined by cells of a squamous cell carcinoma arising in a proximal bronchus Metaplastic cuboidal epithelium lines most of the air spaces (Approximately 200×)

bronchioles rather than alveoli are more likely to be the source of these neoplasms The cells of the tumor have a much closer resemblance to those that line bronchioles, and more specifically the mucus-producing cells, than those usually present in alveoli (Figs. 66–70) When the



Fig 66 Bronchiolar carcinoma A very well-differentiated tumor supported by a thinly septate stroma resembling that of alveolar walls The tall mucus producing cells have basally placed rounded or flat nuclei A mucicarmine stain was positive Mitoses are few Tumors with this structure have been called "pulmonary adenomatosis" by some (Approximately 200×)

bronchioles and their ramifications happen to be met in longitudinal section, the constancy of position in relationship to the order of branching has been noted in many instances (Figs 71, 72) This would suggest an origin *in situ* at these levels, rather than within alveoli or by aspirative spread (47, 7). Hutchison (47), moreover, has pointed out the presence in the distal respiratory passages of epithelium transitional between that which is normal for the region and that of the tumor, likewise in a constant position, usually, neoplastic and histotypical cells abut without transition

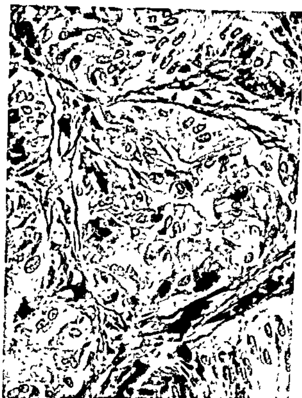


Fig 67 Bronchiolar carcinoma, another instance. Supporting stroma somewhat thicker The epithelial cells are more irregular and occur in several layers The stroma is delicate (Approximately 200X.)



Fig 68 Bronchiolar carcinoma, another instance The variation in the epithelium from field to field is still greater At one end are less tall columnar cells with less vesicular nuclei resembling those that usually line bronchioles (Approximately 200×)



Fig 69 Bronchiolar carcinoma in another instance The cells are highly variable and are in a papillary arrangement The stroma is denser and thicker than in the case illustrated in Fig 66 From the same lung that is illustrated in Fig 62. (Approximately 200×)



Fig 70 Bronchiolar carcinoma The epithelium is closely similar to that of regenerating bronchioles In some fields the columnar epithelial cells possess cilia Compare with the atypical proliferation illustrated in Fig 20 There is, however, evidence of invasion of lymphatics with compression of a vessel (near the upper left-hand corner of the photograph) There is considerable fibrosis, and a heavy infiltration of lymphocytes, plasma cells, and some polymorphonuclear leukocytes



Fig 69 Bronchiolar carcinoma in another instance The cells are highly variable and are in a papillary arrangement The stroma is denser and thicker than in the case illustrated in Fig 66 From the same lung that is illustrated in Fig 62 (Approximately 200X)



Fig 70 Bronchiolar carcinoma The epithelium is closely similar to that of regenerating bronchioles. In some fields the columnar epithelial cells possess cilia Compare with the atypical proliferation illustrated in Fig 20 There is, however, evidence of invasion of lymphatics with compression of a vessel (near the upper left-hand corner of the photograph) There is considerable fibrosis, and a heavy infiltration of lymphocytes, plasma cells, and some polymorphonuclear leukocytes.



Fig 69 Bronchiolar carcinoma in another instance. The cells are highly variable and are in a papillary arrangement The stroma is denser and thicker than in the case illustrated in Fig 66 From the same lung that is illustrated in Fig 62 (Approximately 200×)



Fig 72 Bronchiolar carcinoma Elongated bronchiole, met in almost longitudinal section, the lining epithelium of which has been almost entirely replaced by tumor cells The wall is thickened by invading acini, and by the deposition of fibromuscular stroma containing small mononuclear cells One branch terminates in a series of much smaller channels surrounded by an immense mass of stroma The broad patency of the lumen proximally, the increase in the thickness and presumably in the rigidity of the wall, and the apparently blind termination of some branches, correlate well with the bronchographic findings in this disease as described by Zheutlin, Lasser, and Rigler (58)

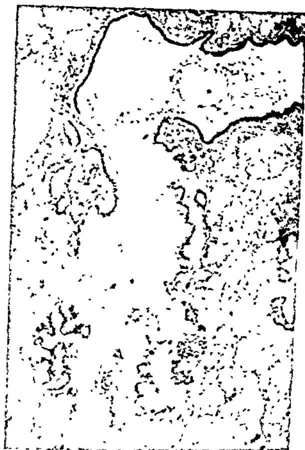


Fig 71 Bronchiolar carcinoma The epithelium of a distal bronchiole is met without transition by the epithelium of the neoplasm that is distributed peripherally along walls of a respiratory bronchiole Compare with Fig 66 from the same patient It is difficult to conceive of tumor originating in alveoli as assuming this relationship to the proximal bronchioles Such an appearance, however, could be given either by aspirative spread, or by the multicentric origin of the tumor in the same region of many bronchioles Field after field in this case reproduces the appearance illustrated.

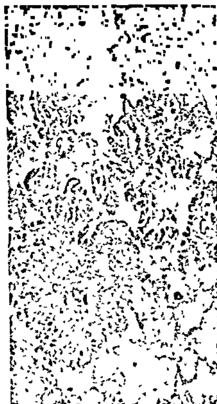


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The question of unicentric versus multicentric origin has been discussed and has important implications for therapy. There is now no doubt that at least some of these tumors do not arise diffusely, for lasting cures have been achieved in some instances by timely resection, when the lesion still appeared to be localized radiographically and at operation



Fig 73 Bronchiolar carcinoma The patient had a history of chronic cough with expectoration of 14 years' duration In February, 1950, at the age of 44, a zone of infiltration in the left lower lobe and some accentuation of vascular markings in the right lung were noted in a chest film

(55, 49, 51). On the other hand, others of these lesions that have been "followed" have shown the persistence of a single focus for a considerable interval of time, followed by spread to other portions of the parenchyma (56) (Figs. 73–77). Certainly the progressive involvement of lung tissue bilaterally is the usual outcome of the disease left untreated, or may even occur after surgical resection, but this is not incontrovertible evidence of multicentric origin It may be explained on the basis of aspirative spread, even when there is no evidence of invasion of the lymphatics, or of extrapulmonary metastasis Storey has wisely stated that the burden of proof lies upon whoever would support the theory of multicentric origin. But this does not rule out the possibility that this

lesion may in some instances be multicentric. Two bits of evidence that have been cited above to support a bronchiolar rather than an alveolar histogenesis, may be taken also to suggest the possibility of multicentric origin: The constant relationship to certain orders of branching of the bronchioles, and the metaplastic changes that Hutchison has considered as possibly precancerous The question of multicentric origin of some of

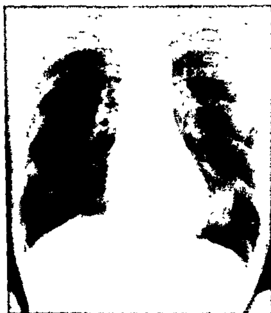


Fig 74 Same patient as in Fig 73 Film of April 27, 1950 A small rounded shadow is now well defined on the right side also.

these tumors thus remains moot, although others certainly arise in one focus

Moreover, one type of "atypical proliferation" that occurs in the course of organizing bronchiolitis and pneumonitis may be similar to the best-differentiated type of bronchiolar carcinoma that in multiple foci is seen widely scattered throughout the lung in such a manner as to make *aspirative spread most unlikely*. *If, then, bronchiolar carcinoma* does arise in such atypical proliferation, multicentric origin is a distinct possibility (compare Figs 20 and 70)

It must be admitted that no sharp distinction has been established and universally accepted between some peripherally situated bronchogenic adenocarcinomas and bronchiolar carcinoma Likely to be classified by

most pathologists as the former, even when the tumor is subpleural and not obviously associated with a major bronchus, would be an undifferentiated neoplasm with relatively few recognizable glands, and one not supported by walls of alveoli and distal respiratory passages. The term "bronchiolar carcinoma" or some equivalent would be applied to rela-



Fig 75 Same patient as in Figs 73 and 74. Numerous minute nodules have appeared throughout both lungs, and seem confluent in the base of the left lower lobe (compare with Fig 76) and in a wedge-shaped zone in the right upper lobe. (Compare with Fig 77)

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diate type there may be a question of classification Perhaps the tendency of late has been to classify too many tumors as "bronchiolar carcinoma," that seem to pursue more closely the rapidly fatal course expected in adenocarcinomas arising in more proximal bronchi

Bronchiolar carcinoma usually presents as a relatively well-differentiated adenocarcinoma supported by thin stroma, generally interpreted as representing walls of alveoli, and distal respiratory passages (Figs. 66, 68, and 71). Upon observation under low magnification, it is indeed evi-



Fig 76 Bronchiolar carcinoma Posterior aspect of left lung shown in Figs 73–75 The mass is seen to consist of multiple nodules that have become confluent on the medial aspect of the lower lobe and just above the diaphragm A small cavity has formed on the lateral aspect of this mass, and a small thick walled pleural pocket is seen to the left of the intrapulmonary cavity Numerous smaller nodules are scattered throughout the lung



Fig 77 Same patient as in Figs 73–76 Many minute nodules are scattered above and below the obliterated fissure separating the right upper and middle lobes The wedge-shaped zone of confluence corresponds to that shown in Fig 75 A small cavity is beginning to form

dent in some instances that the mucous membrane of certain bronchioles has been replaced by the atypical epithelium, and that *it is continuous with that of more distal air* passages, including the alveoli (Fig 62). The wall of the supporting tissue may differ little or not at all from that to be expected at the appropriate level, that is, the muscle and elastic tissue are generally intact, and the connective tissue is not thickened (Figs 62, 71) Caution must, however, be observed in accepting thinly septate stroma as necessarily representing alveoli, since this arrangement *has been noted in lymph node metastases of bronchiolar carcinoma* (Knierim (57), also quoted by Hutchison (47).) Some writers have insisted upon stroma of this type as a criterion of bronchiolar carcinoma (46) *A marked desmoplastic reaction, however, has been observed in* some well-differentiated tumors that behave as do bronchiolar carcinomas in general (Fig 72) Accompanying such a desmoplastic reaction, there may be considerable evidence of exudation, the entire lesion suggesting origin of a neoplasm in atypical proliferation occurring in the course of a pneumonic process (Fig 70).

The epithelium varies from case to case and from place to place within the same tumor. In some, the cells are of the tall, columnar mucus-producing type, occurring in a single layer, with basally placed rounded or flattened nuclei (Figs 66 and 71). To this type the designation "*pulmonary adenomatosis*" *has often been applied and the lesion resembles* the infectious, probably viral, disease of sheep, *jaagsiekte*. Ciliated cells are only rarely observed Mitoses are extremely rare. These atypical cells may abut without transition upon normal ciliated low columnar lining cells of the bronchioles (Fig 71). Hutchison (47) has, however, described intermediate "premalignant" changes In other instances the *epithelial cells are more variable, mucus is scanty or* demonstrable only in an occasional cell, or it may be entirely absent These cells may be quite bizarre, with irregular gigantic forms The epithelium may be in papillary arrangement or in many layers, and may even come to fill the *distal air spaces, while the stroma remains intact* (Figs. 67–69). All gradations between these two extremes exist even within a single tumor Surprisingly, calcification, usually in the form of rounded lamellated psammoma bodies, occurs in almost 50 per cent of the cases, but is usually not extensive and is not demonstrable radiographically. Despite these variations in epithelium there appears to be no correlation with the clinical course, even the best-differentiated tumors, such as have been designated "pulmonary adenomatosis," may metastasize *The lymphatics* have been studied in an effort to obtain a clue as to the mechanism of spread within the lung, and tumor tissue has been found within them in over 50 per cent of these lesions At times, structures (for example, vessels) surrounded by these lymphatics appear to be compressed or even obliterated.

fluence in some foci. In part the gross and roentgenographic appearance of confluence and of vague definition from the surrounding parenchyma is given by mucus aspirated into the air passages even where these are uninvolved by tumor This material may exude in large quantities when the tissue is incised, as a viscid, glairy fluid, and the cut surface may have a

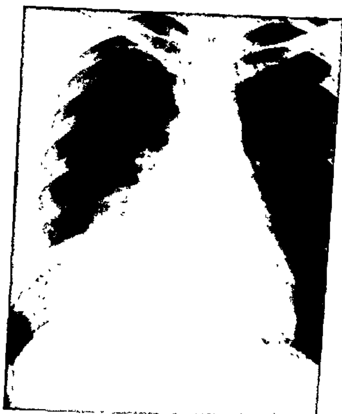


Fig 78 Bronchiolar carcinoma, "diffuse" type Infiltrating process involving the lower portion of the right lung.

gelatinous appearance (Fig 79). In this form, too, massive necrosis is not found, but necrosis may occur gradually with a more subtle crumbling of tissue and loss of substance, so that irregular cavities lined by well-preserved tumor tissue result. These cannot usually be seen in x-ray films

Statements regarding the natural history of these tumors depend upon the criteria employed in distinguishing peripheral bronchogenic carcinoma from bronchiolar carcinoma, and upon whether the experience of a large surgical center, or of an autopsy service, is cited. In approximately



Fig 79 Bronchiolar carcinoma, "diffuse" type From patient illustrated in Fig 78 The resected right lower lobe from a distance appears completely consolidated Much of the consolidation is from mucus aspirated into the parenchyma, to which it imports a translucent glairy appearance and firm consistency



Fig 92 Ovoid mass of homogeneous translucent pink tumor tissue in the apical segment of the left upper lobe There is no evidence of necrosis

25 per cent of instances, the tumor is first detected as a solitary nodule, but more than half of the patients have bilateral scattered lesions when the tumor is first detected. Sequential roentgenographic studies on apparently isolated lesions have demonstrated that some are remarkably stable and exhibit little or no evidence of growth over intervals of some years Thus a young patient reported by Rosemond and his co-workers (55) was observed from 1944 to 1947, whereupon a resection was per-



Fig 80 Upon closer inspection of a portion of the tumor seen in Fig 79, immense numbers of very minute nodules are actually visible These give the appearance of confluence at a distance Microscopically, these nodules are centered upon bronchioles

formed There was no evidence of recurrence three years later The isolated discrete lesion, of course, presents the best opportunity for effecting a surgical cure, and there have now been reported some half dozen patients who have survived in good health for five years following lobectomy or even more limited local resection (55, 49, 51) From data currently available, certain statements regarding prognosis may be made tentatively. It would appear that the pneumonia-like form has a less favorable prognosis than the grossly nodular form. If the disease is multiple, death usually occurs within two years, but if there is no evidence of recurrence within two years after resection, the patient is likely to remain well (51).

The disease spreads within the lung not only by increase of the original lesion, but also very probably by aspiration and by lymphatics (Fig

70). As mentioned before, the possibility of successfully transmitting experimental tumors by intratracheal inoculation has been demonstrated In more than 50 per cent of instances of bronchiolar carcinoma, the lymphatics are obviously involved. In addition, the possibility that the tumor may arise in new independent foci within the lung has not been ruled



Fig 81 Cylindromatous (adenocystic) tumor The line of surgical transection passing through tumor tissue involving the common bronchus of the right middle lobe and right lower lobe is shown Tumor extends into the middle lobe bronchus (upper right), and within the mucous membrane of all proximal lower lobe bronchi

out. Extrapulmonary lymphatic metastases, or hematogenous metastases, are observed terminally, again in approximately 50 per cent of patients. About half of the former are confined to intrathoracic lymph nodes The others are similar to those observed in bronchogenic carcinoma Most patients, however, die in respiratory failure from progressive replacement of pulmonary substance rather than from metastases. Cor pulmonale may also occur.

"Adenomas" and cancer of the lung. There has recently (59, 60) been an outcry against the implications of the term "bronchial adenoma" as it has been generally applied The objection has been particularly

vehement in the case of the cylindromatous ("adenoid-cystic") tumor, as contrasted with the "carcinoid" type The differences between these two lesions have also been emphasized, for example the more central position of the cylindromatous tumor, and especially its frequent position in the trachea or main carina, where the carcinoid tumor is very rarely encountered (61, 7, 62). The greater invasiveness of the cylindromatous tumor, for example of such structures within the lungs as cartilage, is well known, as is the fact that both types are capable of metastasis, largely to hilar nodes, but occasionally to distant organs such as the liver According to a recent review (59), the incidence of metastases in the cylindroid type is 32 per cent, while in the carcinoid tumor it is 9 5 per cent. Prognosis for survival is much better with the latter. This, however, is largely the consequence of the technical difficulty of surgical treatment of tumors that involve, or are close to, the carina of the trachea It has been argued that the cylindroid variety should therefore be considered carcinoma It should be emphasized that the clinical differences between the cylindroid and carcinoid type are largely quantitative, and logically, if the former is to be considered malignant, so also should the carcinoid form

However, these tumors, while not "benign," differ utterly in their development and course from bronchogenic carcinoma The history of symptoms of pulmonary disease is much longer with bronchial adenoma, and may extend over decades, and the curability with surgery is much higher Moreover, the prognosis is little altered by evidence of invasion of such tissues as cartilage, or by the presence of metastases in hilar lymph nodes, and when tumor is of necessity left behind, life may go on for many years (Figs 81–85) Palliative resection to clear the airways may be repeatedly performed Death from widespread metastases occurs in very few patients with these tumors, perhaps somewhat more frequently with the cylindroid than with the carcinoid type (7, 62)

If these differences from bronchogenic carcinoma are clearly recognized, the semantic problem assumes little importance. It is clear that in the scheme of nature there are some neoplasms that differ from adenoma, yet metastasize and invade less vigorously than do most to which the appellation carcinoma is applied To this group belong the tumors that had best be called bronchial carcinoid or cylindromatous tumors, without reference to "adenoma" or "carcinoma"

There are other types of pulmonary tumors that are deserving of the designation "adenomas" One of these has a papillary structure The papillae consist of slender branching extensions of the lamina propria supporting cuboidal or columnar epithelium, with ciliated and mucus-producing elements, and sometimes with foci of squamous metaplasia. Another has a mucoepidermoid structure that resembles that of certain



Fig 82 Section through one of the bosselations protruding into the lumen of the common basal bronchus of the lung shown in Fig 81. The surface epithelium is intact The typical "swiss cheese" pattern of the cylindromatous tumor is demonstrated



Fig 83 Cylindromatous tumor Invasion of cartilage.

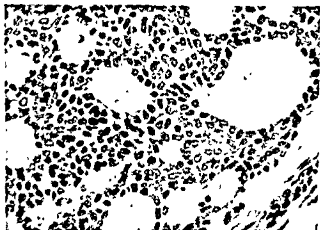


Fig 84 Cylindromatous tumor A higher magnification Multiple lumina are shown in a mass of glands A mitosis is demonstrated near the center of the field The lumen contains mucoid material



Fig 85 Roentgenogram of chest seven years after resection of the cylindromatous tumor shown in Fig 81 Despite the fact that the line of transection during the bilobectomy passed through the tumor tissue, there is no clinical or radiological evidence of recurrence

tumors of the salivary glands (7) (Figs. 86, 87). Malignant variants of the mucoepidermoid tumors also exist.

Sarcoma of the lung. Although responsible for only a fraction of a per cent of all malignant tumors of the lung, sarcomas require brief dis-

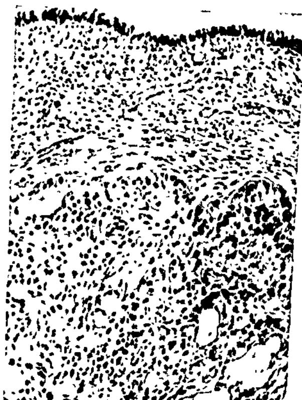


Fig 86 Mucoepidermoid tumor deep in the wall of a bronchus The surface epithelium is intact Large masses of cells surround spaces containing mucus Parts of the neoplasm are similar to epidermoid tumor. This patient has survived eight years to date following pneumonectomy There is no evidence of recurrence (Approximately 100×)

cussion Great care must be taken to distinguish true sarcomas from the polymorphous epithelial tumors. It must also be ascertained that any intrapulmonary sarcoma is, in fact, not metastatic from another site

Two gross types of sarcomas exist. The less rare is a peripheral tumor that appears to have an origin somewhere in the parenchyma (Figs. 88–93). It is this form particularly whose connective tissue origin must be established. The second type occurs in the major bronchi, almost exclusively in the stem bronchi of the lung.



Fig 87 Higher magnification (approximately 200×) of tumor shown in Fig 86 There is considerable variation in the size and shape of the cells Mitoses are rarely found From the histologic features the prognosis cannot be given with certainty

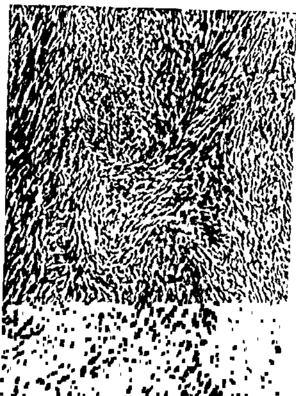


Fig 88 Sarcoma of lung The elongated spindle-shaped cells occur in interlacing bundles There are numerous mitoses.



Fig 89 The margin of the tumor shown in Fig 88 Distal air spaces have become included, and the septa among them consist of massed tumor cells

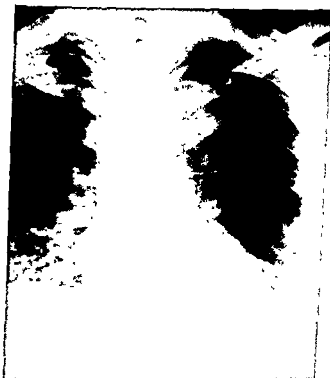


Fig 90. Sarcoma of the lung Same patient as in Figs 88, 89, 92, and 93 Mass in apical segment of the left upper lobe of a 33-year-old man, who had suffered one episode of hemoptysis



Fig 91 Sarcoma of the lung Detail of roentgenogram to demonstrate curvilinear radiolucent zone near the upper margin of the tumor, analogous to 'Cumbo's sign" or the "meniscus sign" as seen in echinococcus disease of the lung Compare with Fig 93



Fig 93 In a more lateral plane of dissection of the tumor shown in Fig 92, a small branch of the apical bronchus is included somewhat tangentially in the substance of the tumor. Near the upper right corner of the photograph is seen a space between the outer capsule and the bulk of the tumor that corresponds to the radiolucent "meniscus sign" shown in Fig 91 The connection with the air spaces was apparently a devious one, and could not be demonstrated by dissection and probing The outer capsule also contains tumor tissue

Sarcomas, especially those that involve the stem bronchi, occur much earlier in life than do the malignant epithelial tumors. According to Iverson's (63) review, the peak age incidence is in the third decade of life. In the case of the peripheral tumors the age incidence has its peak at approximately 45 years. In the central form hemorrhage is frequently a prominent feature of the clinical course, and may be massive, or even fatal The peripheral tumors tend to be more silent in their clinical onset, and the history of symptoms may be as long as seven years



Fig 94 Leiomyosarcoma projecting into the left main upper lobe bronchus and involving an adjacent lymph node There is some hemorrhage, but no grossly visible evidence of necrosis

Grossly, sarcomas are usually composed of soft pale tissue, often streaked with hemorrhage. In the large bronchi, the tumors are polypoid or sessile and tend to obstruct the lumen (Fig 94) Large fragments may be coughed up. Cavitation does not tend to occur in the peripheral tumors, in contrast with the polymorphous cell carcinomas

Histologically, some of these tumors appear to be differentiated into special tissues Some are composed of smooth muscle (64), and consist of [illegible]

sarcoma from pleomorphic cell carcinoma. An osteochondrosarcoma has been reported by Greenspan (65)

The prognosis of the sarcoma appears to be relatively good in comparison with carcinoma The polypoid form in particular tends not to

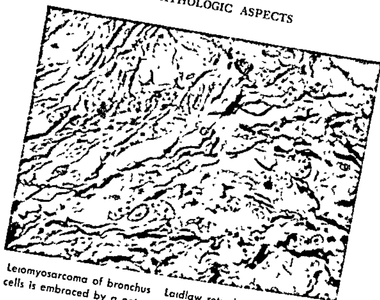


Fig 95 Leiomyosarcoma of bronchus Laidlaw reticulum stain Each of the large bandlike cells is embraced by a network of reticulum fibers

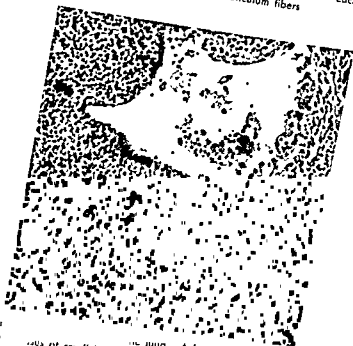


Fig 96 Pri [illegible] e lung A bronchiole is surrounded, but not destroyed, b [illegible] sses of small lymphocytes There was no evidence of involvement of hilar lymph nodes or lymphoid tissue elsewhere Tumor within the lung was localized but not encapsulated (Approximately 100×)

spread beyond the thorax, although local recurrence may occur. Less than 25 per cent of the peripheral forms likewise exhibit extrathoracic metastases

The pulmonary parenchyma may also be the seat of isolated lymphosarcoma that does not, in the earlier stages, appear to be part of a generalized lymphoid involvement. As is generally true of primary lymphosarcoma of organs other than lymphoid tissues, the rate of growth may be very slow, and prognosis appears to be reasonably good, even with rather limited surgical resection such as lobectomy Furthermore, the radiosensitivity of at least one instance has been demonstrated (66)

Most of the patients with this lesion are middle-aged The tumor may be asymptomatic, to be discovered by routine roentgen examination The radiologic appearance and physical signs are those of pulmonary consolidation.

Grossly, the tissue is devoid of necrosis and has a pearly translucency The tissue merges gradually without sharp boundaries into the surrounding parenchyma. Histologically, this appearance is seen to be the result of subtle infiltration of tissue about the bronchoarterial rays, and in the pulmonary and interalveolar septa The component cells are small lymphocytes (Figs 96, 97).

Carcinosarcomas Bergmann, Ackerman, and Kemler (67) have reported tumors wherein both carcinomatous and sarcomatous elements appear to co-exist. These are intrabronchial, sometimes polypoid masses Their prognosis, although established on the basis of very few cases, likewise seems to be more favorable than that of purely epithelial tumors In one unique instance, illustrated in Figures 98 and 99, striated muscle fibers and epithelial cells were intermingled in the tumor, together with undifferentiated tissue All of the elements were pleomorphic and have the appearance of malignant neoplastic cells

Neoplasms of the reticuloendothelial system involving the lung as part of a generalized process Since the lungs not only contain lymphoid tissue, but in fact consist in large part of the reticuloendothelial cells, it is not surprising that they should partake in neoplastic proliferations involving these tissues This involvement is rarely predominantly pulmonary as in some forms of Hodgkin's disease, or in non-lipoid reticuloendotheliosis (Letterer-Siwe disease) In the latter process the lungs suffer not only an infiltration by the neoplastic elements, but there is also a very gradual crumbling, without obvious necrosis, as in the case of bronchiolar carcinoma, so that multiple cavities are formed These are often so thin-walled as to give the lung an emphysematous appearance

Why certain parenchymal sarcomas should pursue a course different from that of lymphosarcomas apparently arising primarily within lymph



Fig 97 Higher magnification (approximately 200×) of tumor shown in Fig 96, to show the almost spherical shape of the cells Mitoses are few Compare with anaplastic carcinoma (Fig 50)

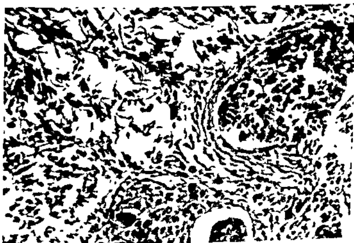


Fig 98 Malignant mixed tumor of lung A field showing grouped anaplastic epithelium and masses of pleomorphic spindle-shaped cells (Printed with the permission of Dr Don Alcott, Pathologist, Santa Clara County Hospital, San Jose, Calif)

nodes, is unknown These tumors as they involve the lung have already been briefly discussed

Metastatic tumors of the lung Since the pulmonary capillaries act as a filter interposed between the systemic veins and the left heart, and since the lymphatic connections of the lung with the mediastinum also are rich, it is not surprising that the lungs should be the seat of metastases even more frequently than of primary tumors

Hematogenous metastases are typically rounded, multiple, peripheral



Fig. 99 Malignant mixed tumor of lung The striations demonstrate the rhabdomyosarcomatous nature of one component of the tumor (Printed with the permission of Dr Don Alcott, Pathologist, Santa Clara County Hospital, San Jose, Calif)

masses Since necrosis occurs frequently, the nodules may become umbilicated. Whenever multiple tumors are demonstrated within the lung, they should first and foremost be considered metastatic, until proved otherwise Occasionally tumor emboli may reach the lung in immense numbers within a relatively short interval of time These then become necrotic and undergo organization The resultant obstruction of the pulmonary arteries may lead to cor pulmonale

Metastases may sometimes present themselves as large isolated masses, occasionally many years after the extirpation of a distant primary tumor This is likely to occur especially with melanoma and hypernephroma Life may be prolonged, or even saved, by resecting such metastatic lesions Confusion with primary neoplasms may occur, since some metastatic tumors may involve bronchi, even of major size This is not rare with tumors metastatic from the large intestine (especially the rectum), from the kidney, and occasionally from other organs

Lymphogenous intrapulmonary spread is typical of anaplastic carcinoma and of bronchiolar carcinoma arising in the lung itself. Metastatic tumors of the prostate and stomach, and occasionally other tumors also, are commonly distributed in the lungs by lymphatics In roentgen films the perivascular markings are accentuated in a radiating fashion, not dissimilar to the appearance of advanced passive congestion.

Spread from one lung to another takes place not only by way of the lymphatics that connect freely across the carina, as well as through the mediastinal rete, but also by means of the bronchial veins. These lead into the azygos vein and thus to the right heart, where redistribution to either lung can occur.

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5

Clinical Aspects

EDGAR MAYER, ISRAEL RAPPAPORT,
AND JOHN LADUE

INTRODUCTION

The early diagnosis of cancer of the lung still presents a difficult problem to both general practitioner and specialist. So far the results in *uncovering the early cases have been disappointing in spite of prodigious* efforts in educating the public and the medical profession, and in the use of widespread x-ray surveys This situation undoubtedly accounts for the present "five-year cure rate" of only 5 per cent.

Discouraging though the present outlook may be, there is ample reason for hope of earlier diagnosis and treatment. Most pathologic changes in the lung lead to clinical manifestations that should be detectable either by x-ray, endoscopy or physical signs. *This requires our improving and* refining available techniques, and developing new methods of examination and case-finding Until a biochemical test is found that will indicate the presence of cancer, we must, if possible, modify our present methods of study so that earlier detection can be a reality

The path toward our objective can be seen from an analysis of the factors that cause delay in diagnosis It is known that more than half of the patients with lung cancer have had definitive symptoms *for nine* months to a year before treatment. Responsibility for this delay falls alike upon both *patient and physician* There are three types of causes for this 1) patients' failure or reluctance to seek medical advice, 2) delayed recognition of "suspicious" evidence by physicians, 3) confusion of concepts about the criteria for truly early diagnosis.

As to the first, it is evident that early diagnosis demands a method of seeking the patient rather than waiting *for the patient to seek the physician* For the most part, patients are not aware of the insidious symptoms *and signs of their early* lung cancer. These can be brought to light only by careful questioning and examinations on the part of alerted physicians. The obvious answer therefore lies in periodic health examinations The need for this has already been conveyed ublic by a ca ign

of education, but obviously this effort must not only be vigorously continued, but also greatly intensified

For earlier recognition of suspicious evidence, the work must begin with the general practitioners. It is up to them to find the potential cancer case among patients whom they examine periodically or whom they often treat for some mild complaints They must be particularly wary of the male patient above the age of 45 who has been a heavy smoker of cigarettes We have incorrectly believed that practitioners have the ability to recognize patients with early lung cancer, and that they can distinguish them from the large number of patients whom they examine because of some trivial illness with common symptoms such as cough, expectoration, chest pain, malaise, dyspnea, wheeze, etc Such discerning ability, if ever developed, can evolve only from years of experience in studying patients with the greatest care, and thereby developing the so-called "high index of suspicion"

To us this much abused term connotes far more than merely bearing in mind that a disease possibly exists A "high index of suspicion" evolves from wide experience in studying detailed histories and correlating them with painstaking clinical and laboratory examinations The knowledge that is gathered in this way, we believe, forms a sound basis for developing this faculty.

Confusion of concepts about the criteria of truly early diagnosis is a common cause of delayed diagnosis It is still widely believed that diagnosis of lung cancer calls for demonstrable evidence of tumor Revision of this concept is long overdue We would urge the acceptance of the idea that the presence of the cancer must be suspected long before the tumor becomes clinically demonstrable. Therefore one must incline toward overinterpretation of symptoms and signs Overinterpretation of history, or of x-ray or physical signs, will thereby point the way to further diagnostic studies, such as bronchoscopy and cytologic study of sputum or of tracheal or bronchial aspirates They should lead to early diagnosis, even though such studies may have to be repeated frequently Only by such experience can we become adept in the application of a "high index of suspicion"

From the foregoing, we feel, an approach toward earlier diagnosis can be developed that should bear immediate results We therefore suggest the following

(1) Case-finding campaigns to be waged on a broad scale with collaboration of general practitioners, public health nurses, and, to a degree, the public All potential cases so uncovered would then be subjected to more intensive screening without delay

(2) Revision of present-day approach to diagnosis based upon the assumption that incipient lung cancer must be suspected before its pres-

ence can be recognized and that diagnosis involves overinterpretation of symptoms and signs before these become obviously manifest.

(3) Application of lessons that can be learned by *a retrospective review* of our medical records and x-rays for study of our *diagnostic errors*, always bearing in mind the question of when and how the diagnosis could have been made earlier, and hoping thereby to develop an increasingly higher index of suspicion.

(4) Increased awareness of the need for—as well as fearlessness of—early exploratory surgery whenever doubt exists

In this chapter, the following clinical aspects will be discussed.

1. Evolution of lung cancer
2. Clinical manifestations
3. Phases of clinical evolution incipient, early, and advanced phases
4. Clinical picture of incipient, early, and advanced phases
5. Clinical features of involved adjacent thoracic structures
6. The commoner extrathoracic metastases
7. Diagnostic procedures and their relative importance
8. Terminal bronchiolar or alveolar cell carcinoma

NOTE An x-ray Atlas illustrating typical and atypical features, with their pitfalls in the diagnostic interpretation of lung cancer, will be found at the end of this book

1. Evolution of Lung Cancer

The clinical manifestations of lung cancer are determined by its character, site of origin, and mode and rate of extension. A brief summary of its evolution will aid our understanding of its signs

Cancer of the lung begins as a proliferation of a few malignant cells in a bronchus, bronchiole, or alveolus Usually the origin is unicentric but occasionally multicentric collections of cancer cells are seen in several bronchioles simultaneously, which can develop into alveolar carcinoma Many workers feel that early in the development of lung cancer, malignant cells do not invade the lung but continue to appear at a particular site (cancer *in situ*) Not infrequently many such *in situ* collections are seen in other parts of the bronchial tree when a well-established cancer of the lung is present nearby Clinically, cancer *in situ* can only be diagnosed when sloughs of tissue are fortuitously obtained and examined by the Papanicolaou method

The multitude of symptoms that may develop once a lung cancer begins to grow depends upon the manner of extension, namely, whether it is: 1) bronchial, 2) contiguous, 3) regional, 4) lymphogenous, or 5) hematogenous. Following are certain of the morphologic criteria of the three phases of its evolution·

Incipient phase. This varies from a cluster of atypical cells in a wall of a bronchus, only recognizable histologically, to the smallest tumefaction detectable by the naked eye

Early phase This begins with the first grossly recognizable growth and includes the first evidence of invasion of adjacent structures, viz., extension of the cancer into the wall of the bronchus or through it into adjacent parts of the lung

Advanced phase This is the stage in which the cancer has obviously spread beyond the primary site of origin and involves the hilar nodes, pleura, or distant tissues

2 Clinical Manifestations

The symptoms and signs of lung cancer will be discussed, insofar as possible, from the point of view of their pathologic physiology. Unfortunately, the earlier stages produce at most minimal disturbance, or none at all, in the normal functions of the lungs. When symptoms do occur they are usually transitory and intermittent, and generally appear only after stress such as results from unaccustomed exercise By the time that a mechanistic explanation of the symptoms and signs is apparent, the disease is often inoperable. Emphasis will be given here to some of the clues that should lead to early diagnosis

The clinical manifestations of lung cancer are most varied, and can and do masquerade as any and all types of bronchopulmonary disease. Most bronchopulmonary diseases present themselves in a characteristic fashion with well-understood clinicopathologic changes, when atypical symptoms and signs occur in such patients, the diagnosis of cancer of the lung should be entertained For example, a patient may present himself with manifestations of chronic bronchitis and at varying intervals will exhibit the clinical picture of bronchopneumonia, bronchiectasis, bronchial obstruction with emphysema, atelectasis, abscess, pleurisy, or empyema The diagnosis of lung cancer may of course be made at any stage, but frequently there is an invaluable lapse of time between the appearance of the first symptoms or signs and the diagnosis We shall accordingly discuss the many clinical manifestations, stressing first the earliest and more common localizing symptoms

Cough When symptoms have arisen, cough is the most common and usually the first to appear In 41.1 per cent of 717 patients reviewed, cough was the first symptom noted and was present in all during the clinical evolution of the disease Cough is so common a symptom in any infection of the upper respiratory tract that it is often ignored for weeks or months by the patient developing lung cancer Unfortunately, many physicians do not fully appreciate the importance of a searching study of the cause of any prolonged cough It is particularly essential to

define its cause in the patient *over 40 or 45 years of age.* The "*chronic* cough" of smokers should never lull our suspicions of lung cancer. Indeed, every chronic smoker's cough should be studied intensively at six months' or shorter intervals. The smoker *who has any change in the* character of his cough should be especially subjected to all the diagnostic procedures for the presence of cancer. Unfortunately, cough is generally a symptom of all forms of pulmonary disease, and its character and pathogenesis are often the same for both neoplastic and non-neoplastic disease.

Cough is a *reflex act, the purpose of which is to keep the airway free.* It is usually involuntary, but may be voluntarily controlled. It is elicited by stimulus of the sensory nerve endings of the mucosa of the respiratory tract. The most sensitive areas extend from the vocal cords to 2 or 3 cm below the tracheal bifurcation. It can also originate reflexly from the pleura, mediastinum, esophagus, and nasopharynx as a result of thermal, chemical, or mechanical stimuli of these structures Both the afferent and efferent pathways are by way of the vagus and glossopharyngeal nerves.

Cough can be defined as a sudden forced expiration against the closed glottis, which is finally opened by *the sudden increment of pressure thus* developed. This force exerted by the muscles of the thorax, abdominal wall, and diaphragm may raise the pressure to 300 mm. Hg or more *Cough is an essential and efficient mechanism* for clearing the bronchopulmonary tree of secretions or aspirated foreign matter that may obstruct the free flow of air It is operative when the self-cleansing function of the ciliary escalator mechanism is unable to cope with the volume of material in the tracheobronchial tree It is obvious that the expiratory pressure must be great enough to move the secretions or foreign matter present Cough will be ineffectual when the peripheral bronchi contain too viscid or adherent secretions, or too large or compact an obstruction. When cough fails to remove the offending substance in the tracheobronchial tree, it may produce further irritation, giving rise to paroxysms of coughing The latter may so increase the intrathoracic pressure that damage to the lungs and ribs, or even vascular injury in the head or chest may result

bronchial tree may be partially or completely obstructed, [illegible] even destroyed by the neoplastic growth. These effects can be produced by growth of the tumor from within the trachea and bronchus or by pressure from without from contiguous involvement of the lung or lymph nodes Cough can result from pneumonitis, bronchiectasis, or lung abscess, distal to the obstructed airway. Involvement of the

pleura, mediastinum, and bony thoracic cage may all be contributing factors The patient with lung cancer may at first cough only on exertion A dry hack at the beginning due to endobronchial irritation becomes increasingly productive as a result of associated infection Narrowing or compression of the trachea or large bronchus produces a hard brassy cough, while advancing bronchial stenosis gives rise to a wheezing expiratory whoop Involvement of the pleura may be associated with a painful dry cough Involvement of the superior mediastinal structures is often associated with a paroxysmal choking type of cough, generally initiated when the patient assumes the recumbent position. Increased activity usually accentuates any of the above forms of cough Other types of cough may develop in lung cancer, but we have described the most characteristic forms The type of cough often affords a clue to the extent and location of the lung cancer

Any unexplained persistent cough, whether characteristic or not, presents an indication for bronchoscopy, repeated cytologic study of sputum and bronchial washings, and detailed x-ray study Recognition of the importance of this may lead to the early diagnosis of lung cancer

Chest pain and discomfort Chest pain is the second most frequent symptom complained of by the patient with lung cancer Twenty and 9/10 per cent of 824 patients gave chest pain as a presenting complaint, but almost 100 per cent developed this symptom sometime during the course of the disease Unfortunately, the less obvious symptom of chest discomfort is rarely mentioned in the reported cases of lung cancer We are convinced that most patients have this complaint early in the course of their disease At onset, chest discomfort is fleeting in character, and later becomes persistent The patient describes it as a sense of fullness, an aching or pressure felt chiefly on the affected side following exercise, change of position, cough, or deep breathing In addition to chest discomfort, intermittent wheezing precipitated by sudden change in weather, walking against the wind, or nervous excitement frequently develop Intensive persistent chest pain is an ominous sign when felt in the shoulder girdle or arm, and usually indicates inoperable disease with involvement of the brachial plexus Severe pain may result from extension to pleura or ribs, or may arise from independent metastasis to the spine

The cause of chest pain and discomfort is often obscure unless there is obvious involvement of the mediastinum, pleura, nerve plexuses, or intercostal nerves Pain can also develop as a result of extrinsic pressure on, or irritation of, the tracheobronchial tree, pulmonary vessels, hilar structures, or nerve tissues, without actual tumor involvement of these structures Accordingly the need for close questioning of patients for any evidence of chest discomfort or pain is obvious

define its cause in the patient over 40 or 45 years of age The "chronic cough" of smokers should never lull our suspicions of lung cancer. Indeed, every chronic smoker's cough should be studied intensively at six months' or shorter intervals. The smoker who has any change in the character of his cough should be especially subjected to all the diagnostic procedures for the presence of cancer. Unfortunately, cough is generally a symptom of all forms of pulmonary disease, and its character and pathogenesis are often the same for both neoplastic and non-neoplastic disease.

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Lung cancer can give rise to all known types and gradations of cough This becomes obvious when it is realized that any portion of the tracheobronchial tree may be partially or completely obstructed, ulcerated, or even destroyed by the neoplastic growth These effects can be produced by growth of the tumor from within the trachea and bronchus or by pressure from without from contiguous involvement of the lung or lymph nodes. Cough can result from pneumonitis, bronchiectasis, or lung abscess, distal to the obstructed airway. Involvement of the

we will now only consider the clinical aspects as they relate to pathologic change

Dyspnea is complained of at some time by the vast majority of patients with cancer of the lung It usually appears with advanced disease and frequently indicates the presence of inoperable carcinoma that has already led to bronchial obstruction, obstructive emphysema, pneumonitis, atelectasis, pleural effusion, or mediastinal involvement with pressure on the carina or trachea

As a first symptom it is rare except in elderly patients Dyspnea on slight exertion or after cough is frequently an early complaint in lung cancer patients of the older age group (60 to 70 years) Since many of them also have some evidence of degenerative cardiovascular disease, evaluation of this symptom may be difficult These patients are often treated for heart disease until advanced malignancy becomes apparent When dyspnea is noted early, it may be a reflex phenomenon and sometimes appears in the form of periodic attacks simulating asthma with or without wheezing, or as periodic irregular breathing with or without chest discomfort Indeed lung cancer patients are known to have been treated for bronchial asthma for long periods of time In the presence of unexplained dyspnea in middle-aged men the possibility of lung cancer should be thought of, even though it is not readily demonstrable

Dyspnea associated with grunting expirations or with attacks of short explosive hacking is often characteristic of bronchial cancer with advanced bronchial obstruction or with increased mediastinal pressure

Dyspnea at rest may not appear until late in the disease, and some patients remain remarkably free of it practically to the end In actual clinical experience it is often just as difficult to explain dyspnea before lung changes appear as it is to account for the frequent absence of dyspnea when there is extensive lung damage The great variation in the individual threshold of dyspnea is an impressive clinical fact This should be borne in mind in the evaluation of every patient, especially in relation to surgical treatment Detailed reference to this will be made in the chapter on functional aspects

Bronchial obstruction A large part of the subjective complaints of patients with lung cancer, as well as many objective findings, are due to bronchial stenosis Its role in the development of cough, dyspnea, and complicating infection has already been mentioned Physical findings due to bronchial obstruction include changes in breath sounds, wheezing, and limitation of motion of lung and thorax Obstructive emphysema, atelectasis, pneumonitis, bronchiectasis, abscess and cirrhotic shrinkage of lung peripheral to obstruction are the resulting pathologic alterations.

Early recognition of bronchial obstruction can often lead to diagnosis of lung cancer in a relatively early stage The patient may have a dry

Expectoration. This symptom is less frequently encountered than cough and was listed as a *first symptom* in 15 per cent of our series of 800 patients, but developed in all patients prior to death from lung cancer. Although not a common first symptom, it is almost always associated with advancing growth along the bronchial wall. Initially, hypersecretion results from irritation due to tumor growth and later develops as a result of infection distal to the obstructed airway. When the bronchus is ulcerated, the sputum may be bloody. Thus, sputum in cancer of the lung can be scant or copious, can appear rusty as in pneumonia, viscid as in mucopurulent bronchitis, or grossly nummular as in bronchiectasis or lung abscess Into these sputa, granulating or degenerating tumors shed neoplastic cells. The importance of cytologic study of sputum and the technique of proper collection cannot be overemphasized These procedures are described in the chapter on exfoliative cytology.

Hemoptysis occurred as a first symptom in 5.9 per cent of 840 patients. If hemoptysis includes blood-staining, the incidence of hemoptysis seen at some period rises to nearly 50 [illegible] is second only to bronc [illegible] orrhage is unusual and [illegible] stages Commonly the patient raises several bloodstained specimens over a period of time. Sudden hemoptysis during the progression of the disease occurred in a little over 5 per cent of patients

Hemoptysis results from erosion and ulceration of the bronchial vasculature by the tumor itself or as a result of associated infection Massive hemoptysis due to erosion of a pulmonary artery or vein by tumor is rare It has been stated that blood-streaked sputum when seen in the early phase of lung cancer is more commonly due to the squamous cell type, however, this is also the most common form of lung cancer and that which most likely involves the larger bronchi The patient with lung cancer who has early hemoptysis is fortunate, since few physicians will permit such a symptom to go uninvestigated. One out of every four patients over 40 years of age who has hemoptysis is estimated to have lung cancer. It is not our purpose to list the multiple causes of hemoptysis but only to insist that every patient who has bloody expectoration be exhaustively studied to rule out the possibility of cancer.

Dyspnea Shortness of breath is of special importance in its effects upon prognosis, as well as being a guide in diagnosis and treatment. Presumably it always represents a disturbance in lung function and as such is to be correlated with the clinicopathologic changes causing pulmonary dysfunction. This aspect of dyspnea will be better understood when discussed on the basis of the derangements of lung function due to pulmonary cancer to which we are devoting a special chapter. Accordingly

tures are still unchanged Partial stenosis leading to early obstructive emphysema is best revealed in the fluoroscopy by characteristic shifts of the mediastinum with the phases of breathing Detailed description of these changes will be taken up under the discussion of fluoroscopy. The x-ray features are most characteristic in advanced bronchial obstruction during the phase of marked obstructive emphysema or in the final phase of retraction of the affected side (See chapter on roentgen diagnosis)

The symptoms of bronchial obstruction have already been partially described The resulting cough is hacking, usually unproductive, and occasionally paroxysmal It probably results from accumulation of secretions difficult to remove at the point of bronchial narrowing Dyspnea is commonly present in patients with bronchial obstruction and may be described as a mild sense of suffocation It is often difficult to distinguish from chest discomfort, which is usually described as a sense of chest constriction Wheezing occurs relatively late as a subjective complaint Expectoration is at first thin and scant, but then becomes increasingly thick and abundant, and is occasionally blood-tinged

Recurrent pneumonitis or *unresolved pneumonia* distal to the point of obstruction is so common a feature that its occurrence in the elderly should lead one to suspect lung cancer Indeed, any pneumonia in a patient over 40 years of age should be carefully studied with serial x-rays When the obstruction has been prolonged, bronchiectasis and lung abscess are the rule On rare occasions the atelectatic edematous lung may undergo cirrhotic shrinkage

It should again be emphasized that bronchial stenosis in its early stages may be compatible with a normal teleoroentgenogram Physical examination, however, uncovers a localized wheeze at some time in 30 to 50 per cent of the patients, and in about 10 per cent this is an early initial symptom and/or physical finding Such abnormalities should lead to bronchoscopic and cytologic studies and early exploratory thoracotomy

In their local extension, cancers of the lung, particularly those originating in the periphery, will often invade the adjacent pleura [illegible] s also involve overlying ribs The [illegible]

[illegible] an indication of advanced [illegible] pulmonary cancer may yet prove resectable and therefore this finding should not of itself contraindicate exploration

Pleural effusion occurs in 25 to 30 per cent of cases and is by far the most common manifestation of involvement of the pleura by lung cancer It was the presenting symptom in 0 7 per cent of our cases Peripheral lung cancers are more likely to involve the pleura early, and are notoriously asymptomatic until they have extended to the pleura This event will be marked by appearance of chest pain as the first symptom,

hacking cough, be subject to mild episodes of asthmatic breathing and wheezing, and yet have a normal x-ray. It should be emphasized that both symptoms and physical signs of bronchial obstruction may be fleeting and transitory, the fact that they are not always demonstrable should not be cause for discarding a suspected diagnosis of lung cancer. Yet it is essential that other causes of wheezing, particularly bronchial asthma, allergic bronchitis, emphysema, bronchial tuberculosis, and cardiac disease be eliminated.

The chest may exhibit slight asymmetry of movement but palpation and percussion are usually normal. On auscultation, diminution of breath sounds and slight prolongation of expiration may be early signs. Careful auscultation may elicit localized wheezing All these findings are more likely to be discovered if the patient is examined after brisk exercise. Mild obstruction offers little or no interference with movement of air at rest but may increase the effort of breathing significantly. After exercise a short whistling sound is often the first indication of a narrowed bronchus If the bronchus is further obstructed, an expiratory wheeze is also heard. Both are more easily elicited with the patient lying on the affected side.

With severe obstruction the wheeze becomes more persistent, may be heard over the entire lung, and is present during both inspiration and expiration Bronchial secretions accumulate at and distal to the point of obstruction, giving rise to coarse rhonchi. As the obstruction becomes more pronounced, expiration becomes prolonged and labored, under the difficulty of forcing air past the obstruction This results in air-trapping behind the stenosed bronchus, producing obstructive emphysema.

When obstruction is complete the affected lung distal to point of obstruction becomes filled with its own secretion. The trapped air behind a stenosed bronchus is absorbed and the lung collapses. The breath sounds are then absent in the involved area, the mediastinum may have shifted to the involved side, and the patient may rapidly develop signs of peripheral infection, the latter leading to the development of bronchiectasis and abscess.

Obstruction of the trachea causes loud stridor, and obstruction in the larger and smaller bronchi causes a wheeze, the intensity of which is usually proportional to the degree of narrowing. The more peripheral the obstruction, the higher pitched are the rhonchi Therefore if obstruction is in the bronchioles, high-pitched musical squeaking rales resembling those of asthma are heard. Bilateral wheeze points to the possibility of tracheal involvement.

Bronchial obstruction can be readily demonstrated by *characteristic fluoroscopic and x-ray changes*. Careful fluoroscopy is particularly important in the early phases of bronchial obstruction when the x-ray fea-

and the neurologic manifestations to be mentioned below deserve increasing attention not only because through them we may detect more of the early lung cancers, but also because thereby important clues may be found as to pathogenesis. This is particularly true of the elusive symptoms of arthralgia, myalgia, and neuralgia which often precede detectable osteo-arthropathy and digital clubbing.

Neurologic manifestations of non-metastatic origin. Localized lung cancer has recently been shown to be occasionally associated with evidence of neuropathy, myopathy, and signs of cerebellar degeneration. Although the association is uncommon, it is of great interest that these neurologic symptoms have appeared prior to any pulmonary or other evidence of the existing lung cancer. Suspicion awakened by such neurologic complaints should therefore lead to a search for lung cancer, and thereby to its early treatment. The appearance of these neurologic symptoms in association with lung cancer is too frequent to be considered as merely coincidental.

3. Phases of Clinical Evolution

The evolution of lung cancer from its incipiency to the patient's death presents infinite variations. Clinical manifestations as previously stated depend upon site, rate of growth, and mode of extension. When the growth is small and confined to a limited area, clinical manifestations are often absent or at the most ephemeral. In some instances, however, a small cancer may give rise to paroxysmal cough, wheezing, and even certain systemic manifestations when the growth is still in its true incipiency. In other instances, close scrutiny and questioning are necessary to uncover any clinical manifestations of lung cancer not demonstrable by x-ray. Nonetheless, it has been shown that early cancers discovered by x-ray surveys have caused symptoms which were usually elicited only when the patients were closely questioned. Furthermore, although the symptoms were not necessarily characteristic, they had been present for a considerable length of time without reaching the conscious level of awareness by the patient. There are many instances of distant metastases from lung cancer giving symptoms that are the first clues to diagnosis. The most striking example in point is the not inconsiderable number of patients in whom brain metastases cause the presenting symptoms. Some of these patients are actually sent to mental institutions and treated for dementia. Others have been operated upon as primary brain tumors, only to find that they represent distant metastases from a small primary lung cancer.

It is true that most patients with lung cancer complain of symptoms and signs too late for successful treatment. Yet there are innumerable instances where the cancer remained localized for months and even on

soon to be followed by increasing chest discomfort, and finally dyspnea when effusion becomes extensive It is worth emphasizing that in patients complaining of chest pain and discomfort the physical signs of early effusion, particularly diminished breath sounds, may be found before the presence of fluid becomes demonstrable by x-ray.

While malignant pleural effusion is often an early clinical manifestation, it usually indicates the presence of an already advanced lung cancer and is ordinarily a sign of inoperable disease. The fluid aspirated is often bloody but can be clear in any stage and occasionally chylous *Hemorrhagic effusions are malignant in nature in about 75 per cent of cases.* Tumor cells are demonstrable in about three out of four patients with malignant pleural effusions. Specific gravity and protein content of the fluid are of little help in the diagnosis

Pleural effusion at times complicates suppurative pneumonitis developing behind an obstructed bronchus. Although the incidence of empyema has decreased since the use of antibiotics, on occasion a small effusion has led to the discovery of operable pulmonary malignancy, since the pleural involvement was infectious and not malignant. Indeed even malignant but localized involvement of the pleura may occasionally prove to be resectable Such "dry" pleural malignant deposits do not therefore contraindicate exploration.

Systemic symptoms. A fact only recently recognized is that lung cancer not infrequently gives rise to apparently unrelated systemic symptoms. These occur frequently enough to be discussed here In the early phase of lung cancer approximately 5 per cent of patients complain of symptoms that can be confused with rheumatoid arthritis. Such patients have joint pains and in addition may develop osteo-arthropathy and clubbed fingers. Not uncommonly, aching of multiple joints and long bones, muscular weakness, sensations of heat and burning in extremities, overgrowth of subcutaneous tissue in the extremities, and/or gynecomastia are confusing These patients have repeatedly been misdiagnosed as having rheumatoid arthritis or endocrine disorders More recently a better appreciation of these phenomena has led to an early diagnosis of lung cancer. Osteo-arthropathy is of course also associated with other types of chronic pulmonary disease, as well as with congenital heart disease, and certain liver and gastrointestinal disorders. No explanation is available to explain the prompt disappearance of these articular manifestations after the resection of lung cancer The most acceptable explanation is that these hypertrophic changes are due to reflex alterations in blood flow of the affected parts

Other systemic manifestations include unexplained anorexia, fatigue, weakness, low-grade fever, mild night sweats often involving the head and neck, and a general sense of uneasiness or apprehension These

than was hitherto believed. Until recently it was assumed that the evolution of lung cancer was rarely prolonged over one or two years. Reevaluation suggests that the period of evolution may be two or three times longer than that. Rarely the disease may last six years prior to death. These facts strongly suggest that the phase of incipiency may be the longest one and that the early phase has a longer duration than the advanced. It should be remembered, however, that the natural history of the individual case may well be determined by host-resistance and biological properties of cell growth. This makes the separation of phases somewhat artificial, but at present we believe it is a useful form of approach.

Ten to 20 per cent of cases of bronchogenic cancers appear to grow more slowly. In such instances the lesions remain localized in the early phase and are found still resectable even though the diagnosis is not made until many months after the first appearance of the lesion. In the remaining 80 per cent, however, experience now indicates that the chances for resectability are poor in spite of what is often referred to as early diagnosis.

4. CLINICAL PICTURE OF INCIPIENT, EARLY, AND ADVANCED PHASES

Incipient phase. If the presence of lung cancer is to be recognized more frequently in the incipient phase, it is necessary to have had a well-organized association existing between patient and family physician for at least a few months or years based on regular periodic explicit questioning together with meticulous physical examinations, in addition to the usual consultations that patients have with family physicians for seemingly trivial complaints. A thorough medical history shall have been well evaluated with emphasis on conditions that tend to persist or recur. Complete data shall have been obtained by repeated questioning and through physical examinations, in order to encompass all past and present ailments in addition to evaluating the present physical status and pulmonary and cardiovascular findings, together with the indicated laboratory, fluoroscopic and x-ray studies. This will necessarily include accurate records as to fluctuations of the state of nutrition, habits of eating, sleeping, and recreation, emotional reactions, indulgence in tobacco, alcohol, and medications, and information regarding so-called trivial complaints such as "cigarette cough," mild respiratory infections, etc.

With such intimate details, the physician with a "high index of suspicion" will be in a favorable position to evaluate any clinical events that may develop in those of his patients whom he may have reason to regard as potential cancer cases because of certain developing symptoms or signs. Consider the male patient aged 45 who has been a heavy smoker

rare occasions for a few years, and yet the lesion proved resectable. Often the patient's tendency to ignore minor symptoms accounts for the frequent discovery of advanced growths at the time of first examination Between the extremes of early and late manifestations there exists every grade of variation in the extent of new growth and the symptoms and signs presented by the patient.

For convenience, we will divide the clinical evolution of lung cancer into three phases, namely, incipient, early, and advanced In the incipient phase the main problem is one of arousing "an index of suspicion" that will lead to diagnosis or justify exploratory thoracotomy. In the early phase, by definition, symptoms and signs of the disease have developed, and the problem exists as to whether the disease is still resectable once the diagnosis has been established. In the advanced phase we are confronted with the problem of palliative treatment and terminal care. This division is necessarily arbitrary since the transition from one phase to the next is often indistinguishable, but it is worthwhile for purposes of discussion and comparison to consider the evolution from the standpoint of these arbitrary periods

The *incipient phase* represents the initial or preclinical period during which the symptoms and signs elicited are merely suggestive. The x-ray shows changes which are questionable deviations from the normal, such as [illegible] or enlargement, local- [illegible] un along the vascular [illegible] and local atelectasis that may be seen to come and go on serial x-rays The patient may complain of trivial cough, slight transient chest discomfort, occasional recurring faint localized wheeze, intermittent vague muscle and joint aches, easy fatigability, and occasional minimal fever Bronchial washings and repeated cytologic studies of the sputum may yield a few abnormal cells It is the discovery of several minimal but more or less distinct abnormalities such as just described, that will lead to early diagnosis.

The *early phase* is established by demonstrating evidence of disease in the lung with localized physical signs, x-ray, or bronchoscopic changes, or by the finding of cancer cells in bronchial washings or sputa. The symptoms and signs can usually be correlated with the location and size of the tumor.

The *advanced phase* presents obvious signs of extension, with bronchial obstruction, involvement of the pleura, mediastinum, or structures adjacent to the lung, or even distant metastasis. There are obvious x-ray, bronchoscopic, and physical findings that permit relatively rapid diagnosis.

This classification into three clinical phases of evolution is further justified by the experience that lung cancers have a much longer duration

sequence of events in these and other cases will be found in the Atlas at the end of this book

Early phase The early phase, by definition, begins when one or more symptoms are associated with objective physical, radiographic, bronchoscopic or cytologic changes consistent with lung cancer By then most patients will have developed annoying enough symptoms, or some signs of the disease In some instances the symptoms experienced by the patients are sufficiently marked to bring them to the physician to seek help In others, survey studies, routine chest x-rays, or the discovery of changing physical signs may lead to a diagnosis of carcinoma of the lung Unfortunately, in most cases, these signals may go unheeded for a long time There is too much procrastination, first on the part of patients who make light of their symptoms, or then by physicians who are loath to take a serious view of apparently trivial complaints that at best are still of doubtful significance Correct evaluation requires more than the cursory history-taking and the usual routine of physical examination and fluoroscopy The physician who is wary of the insidious and treacherous onset of lung cancer will be alerted by some of the varied combinations of early symptoms and signs that frequently warn of the possibility of the disease

The disease may manifest itself by relapsing febrile attacks of mild degree, often described by patients as "one cold on top of the other" Close questioning may reveal, in addition to cyclic recurrence of slight fever, a cough with or without expectoration, malaise with a sense of illness more profound than with similar previous grippe-like infections, and perhaps a persistent leukocytosis These may be followed by increasing fatigability and moderate anemia, with persistent and even progressively elevated erythrocyte sedimentation rate With each recurrent respiratory infection, considerable cough and expectoration can occur Localizing signs in the chest such as changing breath sounds, moist rales, and persistent rhonchi over the affected lung area, may become discernible Evidence of acute pneumonitis may be noted at fluoroscopy and x-ray Although most of this usually resolves soon with chemotherapy, another attack often occurs in the same or adjacent area before the former has completely disappeared The evolution of this clinical picture may be insidious and may develop over a period of months

In another group of patients the clinical evolution of this phase is even more confusing, manifesting itself by a slowly progressive disturbing cough as the first and only symptom Patients who had a chronic smoker's cough previously may now note its changing character The old cough consisted mostly of a clearing of throat, mornings and evenings, or of some cough and expectoration developing with the progress of the day, but going almost unnoticed because both patient and family had become

and who perhaps has recently developed a changing cough, questionable difficulty with breathing, together with variation in breath sounds, a localized wheeze, some loss of muscle tone and skin texture, or suggestive changes in the nail beds Closer questioning may then reveal that this patient also recently began to notice such symptoms as malaise, and recurrent muscle aches and pains suggestive of rheumatism. These complaints and associated physical findings will necessarily call for a satisfactory explanation, requiring close observation. If the cause is a banal respiratory infection, the mild complaints will tend to be transient. If they persist, observation may reveal an aggravation of symptoms and signs, during which repeated chest x-ray or tomographic study is apt to reveal the first appearance of perhaps suspicious streaking, small discrete densities, or an irregularity about the root of the lung in areas where suggestive auscultatory changes may have been heard. This pattern of events should lead to a suspicion of lung cancer in its incipient phase and would call for more detailed study with all available diagnostic methods

Perhaps special emphasis is needed here on the great difficulty of differentiating these symptoms and signs from those due to other causes which the majority of suspect patients of this age group are apt to have Most of them have some degenerative or other chronic disease, and their symptoms, combined with those of the incipient new growth, add immensely to the difficulties. Indeed they are often the cause of failure to suspect the presence of cancer in this stage.

As has been emphasized repeatedly the clinical picture of incipient lung cancer is so elusive that it is almost always missed Many cases accidentally discovered in x-ray surveys are not as incipient as they first appear to be Most of these are not asymptomatic, and detailed questioning reveals that there were significant symptoms for some time. The peripheral lesions are more commonly asymptomatic and have proved resectable in most cases. The asymptomatic peripheral carcinomas are commonly of the adenocarcinomatous type, and because of the higher resectability rate, have a much better over-all prognosis.

There is another group of incipient cases in which the first signs or symptoms are misinterpreted because lung lesions of other associated pulmonary diseases are also present, and can produce similar signs or symptoms For example, a newly developed early carcinomatous lesion in a lung area known to be involved in an old tuberculous process is misinterpreted as a fresh spread of the latter, or a unilateral enlargement of a lung root due to earliest carcinoma is misinterpreted in a patient with old cardiac disease because of a previous bout of congestive failure.

Other similar causes of confusion will be taken up in the chapter on differential diagnostic aspects Case histories with illustrations of the

rapid occlusion. This sequence of events can also be observed in patients in whom the primary growth is in the periphery, but metastases in and about the root of the affected lobe become massive and invade the central bronchi. Since the use of antibiotics, the incidence of suppurative complications of bronchial obstruction has sharply declined.

Pleural effusion, already referred to, is a frequent complication of the advanced phase of the disease. As mentioned before, the clinical picture may occasionally be that of an acute inflammatory pleuritis due to underlying pneumonitis, but more often it is noninflammatory and at times bloody, and usually tends to re-accumulate rapidly following thoracentesis.

Pain and swelling of the chest wall, neck, shoulder, and/or arm may develop as a result of extension of the tumor into the ribs, supraclavicular spaces, brachial plexus, or subcutaneous tissues. The superior sulcus (Pancoast) tumor may involve the base of the neck and invade the upper posterior ribs and brachial plexus, and yet not become clinically evident until pain develops.

If these striking clinical pictures are not characteristic enough of advanced cancer, the *progressive cachexia* which these patients usually develop following the formation of a secondary lung abscess or pleural and chest wall invasion, is plainly revealing.

Migrating phlebitis is not uncommonly seen in association with advancing pulmonary carcinoma and its presence should suggest this possibility.

5. Clinical Features of Involved Adjacent Thoracic Structures

Involvement of adjacent thoracic structures either by the thoracic tumor itself or by its metastases produces some characteristic clinical features.

(a) *Horner's syndrome* (sunken eyeball, drooping upper lid, contracted pupil, narrowed palpebral fissure, temperature and sweating differences between the two sides of the upper part of the body) is an additional feature of the superior sulcus tumor, produced by involvement of the last cervical and first thoracic segment of the sympathetic trunk.

(b) *Vocal cord paralysis* is generally produced by involvement of the left recurrent laryngeal nerve in the mediastinum but occasionally by infiltration of the right recurrent laryngeal nerve in the base of the neck.

(c) *The superior vena cava syndrome* with edema and cyanosis of face, neck, upper thorax, and or arms and distention of veins over upper half of chest and neck, results from obstruction to blood flow through superior vena cava by invasion of this vessel or compression with secondary thrombosis.

(d) *Dysphagia* with the associated symptoms of esophageal obstruction is due to compression by tumor masses in the posterior mediastinum.

accustomed to it. The new cough is now one which persists almost day and night, is apt to come in spells of continued short hacks, and is difficult to tolerate Yet even this may be endured for weeks or months On further inquiry patients or their family will often recall that this hacking had begun many months previously. The patient may wait before seeking advice until he develops increasing and persistent chest discomfort which eventually becomes associated with dyspnea. The advent of an annoying wheeze becoming worse at night and when lying on the affected side, the development of severe pain, or the occurrence of a frank hemoptysis are more urgent reasons for consulting the physician.

In still another group the evolution of the early phase takes the form of an insidiously progressive decline in health associated with loss of appetite, weight, and ability to carry on work, with occasional sweats, palpitation, heat sensations, especially over the extremities, and arthralgia occasionally associated with myalgic and neuralgic pains about the affected joints These patients seek treatment chiefly for rheumatic, arthritic and neuritic symptoms. Among them evidence of pulmonary osteo-arthropathy and clubbing of the fingers may appear, but generally by then the cancer has reached the advanced phase.

The clinical pictures presented by patients in this early phase are therefore exceedingly variable and frequently misinterpreted The common erroneous diagnoses are chronic bronchitis, bronchiectasis, pneumonitis, neuralgia, rheumatic myositis, and arthritis The difficulties which often arise in evaluating these symptoms and signs will be best appreciated by referring to the illustrated case histories in the Atlas.

Advanced phase. By the time the diagnosis of lung cancer is obvious, the disease has become advanced by virtue of extension into the adjacent bronchi, mediastinum, pleura, contralateral lung, chest wall, cervical nodes, or distant organs. Such inexorable growth may lead to a series of complications, some baffling and some quite characteristic

Bronchial stenosis and its sequels, namely, obstructive emphysema, bronchiectasis, lung abscess, atelectasis, and cancrocirrhosis,* have already been discussed. Entire lobes or whole lungs may be involved. The affected part of the lung first appears hyperinflated, then with progressive absorption of the air, shrinkage (atelectasis) develops. Infection of varying degree is the handmaiden of atelectasis. Such infection may eventuate in frank suppuration and abscesses of variable extent or the pneumonitis may finally terminate as extensive fibrotic shrinkage of the cancerous lung. Bronchial stenosis and its complications result from the primary growth extending into the bronchial lumen with gradual or

* A term applied to the progressive contraction with fibrous induration of the lung involved by malignant growth and chronic inflammatory processes

ticularly in the cervical and occasionally in the axillary regions Subcutaneous metastases may occur

7 Diagnostic Procedures and Their Relative Importance

The various means of establishing a diagnosis of lung cancer include a carefully elicited history, a meticulous physical examination, fluoroscopy, a teleoroentgenogram, body section radiography (tomography), bronchoscopy, cytologic studies of bronchial washings, sputum, or aspirated pleural fluid, study of biopsy material obtained by aspiration or excision of accessible nodes, and exploratory thoracotomy

In the *advanced* stage, diagnosis can usually be made readily The history, physical findings, and x-ray are usually diagnostic, and histologic proof is often obtained through various measures mentioned It is important here to define the extent of the cancer which is practically always such that curative surgery is impossible This can be appreciated if all data are carefully reviewed The causes of inoperability in 504 out of 597 patients with proven carcinoma of the lung studied at the Memorial Center for Cancer and Allied Diseases are indicated by Table V

In the *early phase*, diagnosis may be more obscure but use of the various measures available should lead to a correct diagnosis In most of these cases the evidence will be obtained through physical examination, x-ray, and or bronchoscopy In more than 50 per cent, a cytologic diagnosis can be made from sputum, bronchoscopic washings, or biopsies, provided adequate facilities for such examinations are available In the remainder, careful study and evaluation of the history, physical findings, and laboratory studies should indicate enough suspicion of the diagnosis so that exploratory thoracotomy is advised The period of study during this phase should not exceed three to four weeks While this approach will increase the number of exploratory thoracotomies, it will also increase the number of resectable cases.

In the *incipient phase*, a cytologic diagnosis can occasionally be made through repeated studies of sputum, bronchial washings, or "tracheal cough" specimens revealing some suspicious cells The symptoms and physical findings are usually too uncertain in this phase, as has been previously emphasized When the suspected symptoms are persistent and they have some corroboration by x-ray but not by bronchoscopic or cytologic study, diagnosis can only be made by exploratory thoracotomy There is rarely justification for delay after watching an x-ray shadow which persists for about a month in spite of antibiotic therapy To achieve such earliest diagnosis we again emphasize the need of active co-operation between the whole team of family physician, internist, roentgenologist, bronchoscopist, pathologist, and surgeon.

(e) *Cardiac manifestations* including pericardial effusion, tachycardia, arrhythmias, or congestive heart failure developing usually as a direct result of invasion of the pericardium or myocardium Cardiac involvement by direct extension or metastases is a common finding at autopsy that often escapes clinical recognition.

(f) *Phrenic paralysis* is indicated by progressive elevation of the diaphragm and a tendency toward paradoxical movement

6. The Commoner Extrathoracic Metastases

Clinical manifestations due to extrathoracic metastases may often predominate or contribute significantly to the clinical picture of advanced lung cancer Practically all parts and all organs of the body may become the site of metastases The percentage of metastases reported in different organs varies widely in the reports in the literature. Undoubtedly the more meticulous the pathologic search, the more frequently are metastases likely to be found This applies particularly in an organ such as the brain which is not routinely examined in some post mortems Among the more common distant metastases are the following

(a) *Cerebral metastases* have been reported in the widely varying frequency of 40 to 50 per cent. Involvement of the central nervous system produced the presenting symptoms in 4 per cent of cases in one study. These metastatic lesions may simulate the clinical picture of rapidly growing primary brain tumor. The need to exclude primary lung cancer before operating on brain tumors and in the differential diagnosis of disease of the central nervous system is now well recognized Recent evidence indicates that the vertebral veins draining the posterior mediastinum are the most likely avenues of metastatic spread to the brain and central nervous system Metastases to the brain are obviously to be expected inasmuch as cancer cells are carried directly by the blood stream to the brain without passing through the pulmonary capillaries

(b) *Renal metastases* are found at autopsy in 16 to 40 per cent of patients with cancer of the lung A similar incidence of metastases is reported to involve one or both of the *adrenal* glands and infrequently may cause an Addisonian crisis

(c) *Bone metastases* have been reported in 17 to 34 per cent of patients dying of cancer of the lung. They occur most commonly in the spine, rib, skull, and long bones Occasionally the presenting symptoms of lung cancer are due to the bone metastasis.

(d) *Liver metastases* occur in 30 to 50 per cent of patients dying of lung cancer, but are usually a late manifestation of the disease

(e) *Other metastases* may at times be noted in almost every organ of the body Frequently one finds multiple lymph node involvement, par-

chial obstruction When stenosis is minimal, there may be almost no abnormal physical findings, when marked, a wide variety of signs may be evident

Partial occlusion of a bronchus results in obstructive emphysema giving rise to diminished motion and distant breath sounds on the affected side Localized or unilateral wheezing is a frequent and important sign. Fine, medium, or coarse râles can be elicited over the lung aerated by the narrowed bronchus When a main bronchus is involved, the mediastinum may be seen to move toward the involved side on deep inspiration and to the opposite on forced expiration When the bronchus is totally occluded, atelectasis with dullness and absent breath sounds is found over the involved lung, and the hyperresonance of compensatory emphysema is noted over the uninvolved lung Such atelectasis may be due to obstruction at the site of tumor due to trapped secretion The degree of obstructive emphysema or atelectasis may vary from time to time depending upon the degree of obstruction After the release of secretions through cough, postural drainage, or bronchodilators, atelectasis may temporarily disappear

In the advanced stage involvement of other structures in the thorax may give rise to striking physical findings These as mentioned include the signs of superior vena caval obstruction, Horner's syndrome (with other characteristic physical signs of a superior sulcus tumor), vocal cord paralysis, elevated and immobile hemidiaphragm, esophageal obstruction, and signs of invasion of pericardium and myocardium

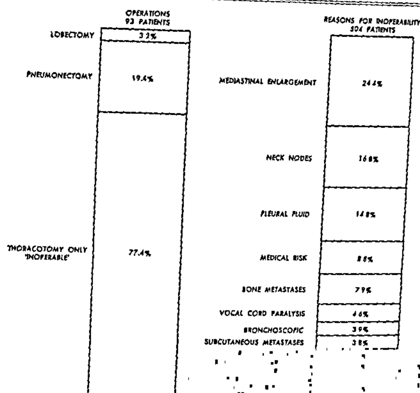
Inspection alone may be rewarding to the examiner in the detection of abnormal physical signs if the patient is carefully observed. Clubbing of the fingers, dyspnea, and cyanosis will focus his attention on the chest Displacement of the mediastinum can be suspected when the cardiac apical impulse is displaced If expansion of the chest is limited on the side towards which the mediastinum is displaced, atelectasis may be suspected If expansion is impaired and if the corresponding interspaces are bulging, pleural effusion may be suspected, and not uncommonly, the trachea, heart, and mediastinum are displaced to the opposite side

Obvious venous distention of the head, neck, upper thorax, or arms with variable edema of the same structures suggests inoperable lung cancer due to invasion of the superior vena cava or innominate vein

Palpation is particularly important in detecting metastatic nodes in the supraclavicular region, neck, and axillae The finger tips are used in massaging movements along both sides of the neck, penetrating deeply into the supraclavicular fossae and up into the pits of both arms as well as along the axillary intercostal spaces Subcutaneously palpable tumor masses anywhere over the chest may be signs of metastases Palpation may further reveal a displaced trachea or apical cardiac impulse, de-

TABLE V

INCIDENCE OF OPERABILITY



Physical findings We have purposely delayed discussing the physical findings until the over-all picture of lung cancer had been presented At this point we believe their description will more clearly indicate their importance in diagnosis. In the incipient phase we have shown that the physical signs of lung cancer will most likely be absent, in the advanced stage they may be present in such confusing abundance as to seriously mislead the unwary. In the early stages they may or may not be marked Again, their absence does not preclude the presence of lung cancer and their evanescent character in some early cases unfortunately may cause prolonged temporizing One of the chief values of early physical signs is that when detected and not explainable they will at least prompt the examining physician to resort to x-ray studies

In the early and advanced phases the variety of physical findings in the chest depends largely upon the presence, degree, and duration of *bron-*

be essentially normal. Systematic and meticulous fluoroscopy should be practiced as a part of every medical examination. It supplements both the physical examination and x-ray, by affording observation of the movements of the chest and the structures within it in relationship to one another.

Fluoroscopy is of real value in the diagnosis of early lung cancer of major bronchi, which so often leads to obstruction when the stenosis begins to interfere with the free flow of air on one side of the chest. With respiration this will be reflected by changes in position of the mediastinum, producing so-called mediastinal shift. As air flow lags in the blocked lung, it will fail to expand and retract simultaneously with the normal lung, thereby causing the mediastinum to shift toward the affected side on inspiration and toward the normal side on expiration. These shifts are elicited better with deeper and stronger respirations. Sudden inspiratory sniffing will cause "mediastinal jerk" toward the affected side, while cough will exaggerate the shift toward the normal side.

With increasing bronchial blockage, first obstructive emphysema, and later, retraction of the affected lung will develop. Obstructive emphysema is revealed on fluoroscopy by a mediastinal shift away from the affected side which remains expanded in expiration, the diaphragm on the same side remains in the low inspiratory position, while the diaphragm on the uninvolved side descends and rises as usual with breathing. This results in a seesaw paradoxical motion of the diaphragm. The bronchi dilate on inspiration and contract on expiration, so that an obstruction occluding part of the lumen during inspiration may completely occlude it during expiration and trap the inspired air peripheral to the bronchial obstruction. The trapped air gives rise on expiration to increased translucency of the lung peripheral to the obstruction. In advanced disease, with complete blockage and retraction of the affected lung, there is permanent shift of the mediastinum toward the affected side. The diaphragm on this side will be displaced upward.

Fluoroscopy is of special value in the early recognition of small pleural effusions at a time when these may not yet be demonstrable on the x-ray. Minute collections of pleural fluid discovered on fluoroscopy will stimulate the physician to make an exhaustive study of the patient and may often lead to discovery of malignancy.

In deciding upon operability, fluoroscopy can play an important role in the patient with apparently advanced cancer. It will uncover paralysis of the diaphragm and may indicate fixation of the structures along the mediastinum and in the root of the affected lung. Both are generally indications of unresectable cancer. However, diaphragmatic paralysis due

creased or absent tactile fremitus over an involved lung, coarse rhonchi over an obstructed bronchus, tenderness of involved ribs or sternum, especially elicited *on pressure, and a large nodular liver* possibly indicative of metastatic disease.

Percussion may elicit signs of dullness or flatness due to atelectasis, pleural thickening, or fluid. Occasionally a large tumor mass may give a flat woody percussion note. Hyperresonance is often elicited with obstructive emphysema. Displacement of the heart and widening of the mediastinum may be detected by percussion.

Despite our strong emphasis on the value of the x-ray in pulmonary disease, the stethoscope can still play an important part in detection of lung cancer. On *auscultation, diminution of breath sounds over one or* more lobes with localized wheezing should suggest in the aged the possibility of cancer by indicating bronchial narrowing. Fluctuating rales that are heard on one examination and are absent on another require further study. Absent breath sounds may indicate complete bronchial obstruction or pleural effusion. Large tumors may give rise to localized bronchial breathing, transient bronchial breathing suggests recurrent *pneumonitis*. In *general, we may say that a combination of varied* auscultatory physical findings with a tendency to change from day to day, and with no known disease to otherwise account for them, should at least suggest the possibility of lung cancer.

Laboratory tests for patients suspected of cancer of the lung should include 1) those determinations which are an integral part of any complete medical examination, 2) special examinations which may aid in *establishing a diagnosis of pulmonary cancer, such as cytology*; 3) search for possible metastatic disease, and 4) tests to determine the adequacy of pulmonary function (see chapter on functional aspects). In the discussions on the clinical and differential diagnostic aspects of lung cancer as well as in various specialty chapters, reference is made to tests which may be of diagnostic aid. It merely remains, therefore, to comment briefly here on certain points not mentioned elsewhere.

Anemia is rare in uncomplicated bronchogenic carcinoma but may be caused by the secondary infection or metastatic disease.

Leucocytosis of varying degree is common, due to superimposed infection. Occasionally a very high white count is noted, this requires differentiation of a leukemoid reaction from true leukemia.

Erythrocyte sedimentation rates may vary *widely and are of little value* in differential diagnosis.

An elevated alkaline phosphatase suggests the possibility of bone or hepatic metastases, if not explained by other disease conditions.

Fluoroscopy Fluoroscopy may occasionally lead to suspicion of malignant pulmonary disease even when a routine chest x-ray is reported to

be essentially normal Systematic and meticulous fluoroscopy should be practiced as a part of every medical examination It supplements both the physical examination and x-ray, by affording observation of the movements of the chest and the structures within it in relationship to one another.

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to involvement of the phrenic nerve does not necessarily preclude operability

Although fluoroscopy is invaluable when used with full appreciation of its limitations, it becomes dangerous when too much reliance is placed upon it in the search for small and discrete changes in the periphery and particularly at the roots of the lungs. We emphasize that practitioners who use fluoroscopy alone in place of x-ray are apt to miss opportunities for early diagnosis

The teleoroentgenogram. For the diagnosis of lung cancer by x-ray as well as for the technical aspects of the various modalities used, we refer the reader to the special chapter on the subject. The role of x-rays in the diagnosis is of such overwhelming importance that even at risk of repetition, we will present here some of the more significant aspects as they relate to the clinician

The clinician must realize the limitations of x-ray in the diagnosis of incipient lung cancer when slight or transient changes may appear very indefinite or may be misinterpreted. Furthermore, in the early and advanced stages, the roentgen features are often indistinguishable from those of other pulmonary diseases Therefore the entire clinical picture must be taken into account in the evaluation of the x-ray findings

To detect the earliest changes, as was stated before, every male patient of 45 years and over should be x-rayed at least every six months with careful serial comparison of all films Meticulous attention should be given to the minutest variation from the normal even though this may lead to overinterpretation The important early x-ray lesions include a peripheral nodular density (often having a notched border, especially when defined by tomography), infiltration or streaking along the vascular trunks, unilateral enlargement or irregularity of the hilum, segmental or lobar emphysema, atelectasis, and, rarely, early abscess formation

The x-ray is a most revealing method of study for an investigation of cough, wheezing, chest pain, dyspnea or hemoptysis Evidences of early and advanced lung cancer are most readily found by x-ray, but the detection of incipient lesions demands the utmost skill of both roentgenologist and clinician. The x-ray may vary from day to day in a striking fashion, depending, as we have stated, upon the degree of bronchial obstruction and the amount of trapped secretion. A so-called typical x-ray feature of lung cancer is difficult to define and not to be relied upon as the sole diagnostic feature

Since approximately half of all lung cancers have their origin in the first 4 to 6 cm. of the main bronchi, the tumor frequently presents itself as a unilateral density near the hilum It is often roughly triangular in shape with the apex pointing outward and apparently giving rise to strand-like processes radiating toward the periphery. Atelectasis or collapse

of the lung segment supplied by the obstructed bronchus appears as a sharply delineated density Once the obstructive element is established, infection of varying degree frequently develops distal to the stenosed bronchus and manifests itself roentgenologically as a pneumonia. In the aged a frequently recurring pneumonitis or one failing to resolve should always suggest the possibility of cancer.

Associated bronchitis may evidence itself on x-ray as increased bronchovascular markings, and occasionally the central lesion may be overlooked. With partial occlusion of a bronchus, obstructive emphysema may manifest itself as a large area of increased translucency distal to the narrowed bronchus With prolonged obstruction and recurrent infection, resultant bronchiectasis presents wedge-shaped densities at the costophrenic angle or in the periphery of the lung Central necrosis in a large tumor may give the x-ray appearance of a lung abscess Combinations of any of the above features with that of a pleural effusion are not infrequent in advanced cancer

Peripheral lung cancer shows up as a round or irregular shadow of variable size Small solitary cancers are frequently mistaken for metastatic deposits, tuberculosis, or unresolved pneumonia. When all of one or more lobes is involved, the x-ray shadow is indistinguishable from other types of lobar consolidation All gradations from the small to the larger coalescing and lobar densities can be seen in the x-rays of any large series of lung cancers The roentgenologist frequently has difficulty distinguishing between central and peripheral disease, but often lateral chest x-rays help make the differentiation Infection is frequent in cancer and confuses the x-ray diagnosis by superimposing the pictures of bronchopneumonia, lobar pneumonia, bronchiectasis, and lung abscess. The longer the duration of lung cancer, the more difficult the task of deciding by x-ray whether or not the disease began centrally or peripherally

Body section radiography, variously called tomography, laminagraphy, and planigraphy, has provided us with a means of visualizing in greater detail the mediastinum, lungs, and tracheobronchial tree in the anteroposterior, lateral, and oblique planes By focusing the x-rays at different depths in the thorax, shadows of the disease process at various levels that otherwise may be overlooked can be visualized and also better evaluated as to character of their density, such as calcifications, hard rounded nodules, etc. Such information combined with bronchoscopic data permits a fairly accurate preoperative estimation of the size, extent, and exact location of the cancer, as well as its relation to other thoracic structures Tomography not uncommonly reveals metastatic cancer and inflammatory lesions in the lungs which cannot otherwise be seen on routine teleroentgenograms This x-ray procedure has proved extremely

valuable not only to the thoracic surgeon but also to the physician responsible for making the diagnosis.

Bronchoscopy. A bronchoscopy is a mandatory procedure in a patient suspected of having a centrally located lung cancer. *A negative bronchoscopic finding does not by any means exclude lung cancer.* The location of an abnormal x-ray shadow is one of the chief guides to the potential significance of a positive or negative bronchoscopic examination. With positive bronchial biopsies the number of operable cases decreases considerably

considerabl

evidences o

we refer the reader to the chapter on bronchoscopy.

Exfoliative cytology. Combined examination of bronchoscopic washings and freshly raised sputa by the Papanicolaou technique for detection of cancer cells has afforded a preoperative pathologic diagnosis of lung cancer in many cases when expert cytologic facilities are available. The number of positive diagnoses derived from the study of bronchial washings or of sputa alone varies greatly among the many reports. The number of false positives is extremely low in experienced hands. We refer the reader to the chapter on cytology for details.

Bronchography has been said to be helpful in the diagnosis of certain bronchogenic cancers. It may occasionally be so when the tumor fails to cast an x-ray shadow or when it cannot be seen by bronchoscopy or tomography. However, deformation or narrowing of the lumen of the bronchus can only occasionally be demonstrated and the failure of a bronchus to fill is not always due to a suspected tumor but may be caused by trapped bronchial secretions, stricture, or a foreign body. Furthermore, aspiration of lipiodol into the opposite lung carries the risk of seeding cancer cells. Therefore, bronchography in general has been of such little value that we believe it had better be abandoned except in unusual circumstances.

Angiocardiography. Angiocardiography may prove to be useful in the differential diagnosis of lung cancer. Any space-occupying lung lesion may narrow, displace, or obstruct the pulmonary or mediastinal blood vessels. Obstruction or irregular deformation of the opacified vascular structures of the lungs or mediastinum is most commonly due to neoplastic disease. It must also be kept in mind that lung cancer may cause only simple dislocation of the vascular structures particularly when the disease is circumscribed or peripherally located. Angiocardiographic evidence of incurable carcinoma of the lung depends upon local invasion of the great vessels of the lungs near their origin. Partial or complete obstruction of the left pulmonary artery near its origin, or of the right pulmonary artery at and near its first bifurcation, obstruction of the

great mediastinal veins by tumor, or evidence of pericardial invasion seen as a thickening of the pericardium, are not infrequently seen with this technique The interpretation of angiocardiograms requires an experienced worker in the field.

Aspiration biopsy of the lung The indications for employing this method of diagnosis are very few. If a positive biopsy is not obtained by bronchoscopy or after study of bronchial washings and/or sputa, exploratory thoracotomy is resorted to in preference to lung aspiration This is especially true if there is any likelihood that the disease is operable. Occasionally, however, aspiration biopsy may be used for diagnosis in the inoperable case. Its chief field of usefulness is in the superior sulcus carcinomas and cancers which present a large, broad anterior mediastinal mass. Tumor growth along the needle pathway is a calculated risk We believe this diagnostic procedure should not be used unless the patient refuses thoracotomy or has inoperable disease Negative lung aspiration does not prove the absence of lung cancer

Biopsy of metastatic lesions In 199 patients studied at the Memorial Center the diagnosis of lung cancer was made by excising or aspirating metastatic disease in accessible regions such as neck nodes, ribs, subcutaneous nodules, or even liver nodules A microscopic diagnosis was made in 66.8 per cent of these patients, an additional 29.1 per cent yielded specimens which were obviously cancer but with unknown origin Study of pleural fluid in 24 patients by the Papanicolaou technique revealed cancer cells in 69.0 per cent of the patients and was negative for cancer in 30.9 per cent (see Fig 100) The indications and technique for scalene node biopsy are discussed in the chapter on surgical therapy

8 TERMINAL BRONCHIOLAR OR ALVEOLAR CELL CARCINOMA

One and one-half to 5 per cent of lung cancers present the microscopic picture of bronchiolar cancer which may show symptoms and a clinical course somewhat different from other types of lung cancer. Dyspnea may be a prominent symptom Expectoration, especially of a glairy or mucoid type, is more common, being recorded in more than half of the cases, and is sometimes profuse. Death may occur in less than six months in as many as 30 per cent of the patients, but it is usually a slowly progressive chronic disease, not debilitating until late in its course and giving rise to very few early symptoms This disease also differs in that about 50 per cent exhibit involvement of both lungs Cases in the 20- to 40-year age group are not rare

The physical findings are not definitive and indeed may be minimal even in the presence of the bilaterally disseminated forms The most common radiographic picture is the finding of single or multiple peripheral, circular areas of increased density bearing a striking resemblance

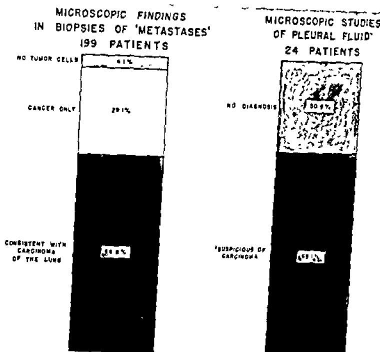


Fig 100

to either tuberculosis or metastatic tumor. Not infrequently in the multiple nodular cases diagnoses such as pneumoconiosis, miliary tuberculosis, collagen disease, or metastatic cancer are made Cytologic studies of sputum tend to show cancer cells in a relatively high proportion of patients The tumor is rarely visualized bronchoscopically

The treatment is disappointing except in the patient who has a single peripheral nodule and in these individuals a 40 per cent five-year survival has been reported after surgical resections When the disease is disseminated neither x-ray nor nitrogen mustard has offered much palliation

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6

Roentgen Diagnosis of Lung Cancer

ROBERT S. SHERMAN

CRITICAL ANALYSIS OF THE ROENTGEN METHOD IN RELATION TO THE DIAGNOSIS OF LUNG CANCER

The roentgen diagnosis of lung cancer is so extensive a topic that a complete presentation in the conventional manner would not be feasible in a chapter of this length. Furthermore, it is believed that this subject has largely outgrown the atlas format which at best suffers certain rather serious limitations. What will be attempted, therefore, is the perhaps more difficult task of selecting and organizing information that will provide understanding and insight into the roentgen diagnosis of malignant lung tumors. Just as the critic need not be an accomplished performer in the arts, neither should the generalist, internist, surgeon nor other specialist feel required to become a practicing roentgenologist. However, although these physicians do not need to know how to practice diagnostic roentgenology, they must nevertheless become thoroughly acquainted with its accomplishments and newer developments, as well as its limitations and pitfalls, so that they can critically appraise it and thereby be in a position to ensure that their patients always receive x-ray work of a high order.

In a presentation of this sort many aspects of roentgen diagnosis will have to be omitted, and for the purpose of orientation they will be noted at the onset. The most important of these are. 1) the physical basis of the roentgen method, 2) normal roentgen anatomy and physiology of the chest, 3) radiation exposure and dosage; 4) the roentgen appearance of the various histologic types of lung cancer, 5) differential diagnosis; 6) postoperative appearance of the thorax.

Roentgen diagnosis is an act of medical practice and not a laboratory procedure. In the latter, results are reported by reading markings on a scale or noting a color change in a solution, each taking place after the performance of a number of standardized steps requiring no formal medi-

cal knowledge for their execution. On the contrary, diagnostic roentgenology is a branch of clinical medicine in which a broad medical background, specialized training, and experience are necessary features. The results of an x-ray examination are expressed not in figures but in terms of disease, and constitute a medical diagnosis or judgment on the part of the roentgenologist for which he is responsible to the patient.

Competent x-ray diagnosis in lung cancer is founded upon the belief that the disease is curable if discovered early, and that efforts directed to this end are therefore necessary and urgent. The earlier the disease can be identified, the better is the chance for palliation. Unless these tenets become a constant guide, the examiner's attitude will not be sufficiently aggressive and it may permit him to become a willing partner to the insidious practice of resorting to interval studies over an uncontrolled period of time in attempting to arrive at a diagnosis.

While there is always room for individual experience and ability to manifest itself, a general uniformity of opinion from a group of experienced and competent roentgenologists is nevertheless to be expected. In other words, there is a certain acceptable standard of performance in *diagnostic roentgenology, just as there is in any other branch of medicine.* While specialty certification may be a clue regarding the existence of such a level in any individual, this is not necessarily so nor is it particularly true in the field under consideration. Additional insight into the actual level of the acceptable standard in x-ray diagnosis is provided through texts and current medical articles, as well as by attendance at x-ray conferences and meetings.

An appreciation of the dynamic aspect of roentgen diagnosis in lung cancers is another requirement. The picture provided by roentgenology at one particular time must always be related to the known life history of malignant lung neoplasms, including the development of complications and the effects caused by treatment. In this connection physicians should always keep in mind that since it is so common today for patients to have had chest roentgenograms, every effort should be made to secure all previous films for comparison purposes once a lesion has been discovered, not only to further the diagnosis, but to learn more about the development and course of this important disorder.

The qualified examiner will tend to go from the simple preliminary x-ray studies, through a logical and orderly sequence, to the more complex. To be able to do this he must possess an equal facility with all the techniques of roentgen diagnosis, and his usage of the different examinations must be based on a knowledge of what each may be expected to accomplish, not upon a personal preference for some particular one. When little or no worthwhile results are likely, additional examinations must not be recommended, for every roentgenologist is morally bound

to the patient to justify each roentgen procedure and to make it as safe, simple, and inexpensive as possible. At times this principle may bring him into conflict with those who through misguided concepts either ask for all possible examinations or insist on overemphasizing some pet technique.



Fig 101. There is a mass in the right lung, with deposits of tumor in the right side of the mediastinum and a small metastasis to the left lung in the infraclavicular region This is a squamous carcinoma of the lung

Ideally every x-ray study should be carefully integrated with the clinical progress of the case. The selection of the proper roentgen procedure and its correlation with the patient's clinical management call for experience and good judgment. In this regard the roentgenologist should be familiarized with the thinking of the patient's physician regarding operability, resectability, operation for palliation, and radiotherapy, as well as his attitude regarding the x-ray criteria of non-resectability. At the present time not all of these considerations have become standardized,

so that ideas may vary somewhat from clinic to clinic and from physician to physician

Making allowance for the fact that the status of the purely palliative operation remains debatable, certain criteria strongly indicating non-re-

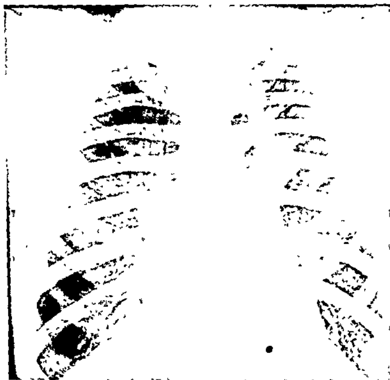


Fig 102 An irregular patchy infiltrate in the left infraclavicular area is seen which gives a roentgen appearance resembling an infection of the lung Tuberculosis may present such a pattern No obvious disease is shown in the left lung root or mediastinum This is a squamous carcinoma of the lung

sectability have nevertheless become generally accepted Those relating directly to roentgen diagnosis are bilateral pleural fluid, metastases to the opposite side of the thorax, or outside the chest, or the tumor crossing the carina Roentgen evidence of probable non-resectability such as unilateral pleural effusion, diaphragmatic or vocal cord paralysis, extensive mediastinal disease, local invasion of the chest wall, and vessel narrowing, do not always deter the more aggressive surgeons who feel that one cannot be certain of non-resectability under these conditions unless they

actually try to remove the lesion It should be apparent that the justification for the use of various roentgen examinations depends on the surgeon's attitude in these matters For example, there is no need to carry out contrast visualization of the heart and great vessels to determine resectability, if the surgeon does not heed the findings obtainable thereby.



Fig 103A

The terms found in a roentgen report sometimes leave much to be desired because they may be confusing or even misleading. One way to help change this situation would be for physicians to challenge obtuse and misleading words or opinions. Disease processes in roentgenology of the chest are revealed either by a morphologic alteration, in which case there is an abnormal density change, or they are physiologic, and seen as a variation in the normal function of the chest or its organs In cancer of the lung, both forms of abnormality are encountered. In the first category, which is by far the more important, only a few easily understood attributes are possible. These deal with size, shape, borders,

degree of density, location, and internal pattern or texture Each one can be described in a simple manner. Size must always be stated in universally understood units such as centimeters or inches. Designations such as small, large, huge, or massive should be abandoned as lacking specificity.



Fig 103B

Fig 103A and B A tumor is seen in the anterior segment of the right upper lobe with a focal atelectasis in the middle lobe The right lung root and mediastinum appear to be normal and the esophagus reveals no pressure defects This proved to be adenocarcinoma of the lung

Localization should be based on the practical needs of the situation and should employ the standard anatomic terms that all physicians understand Once a functional alteration has been revealed, its description is usually a simple matter of recording the degree.

Occasionally the x-ray findings may justify a precise diagnosis, such as a certain histologic picture, specific bacterial agent, or a physiopathologic state Usually, however, the presence of a more or less general category of disease is all that can be concluded Overinterpretation of the

roentgen findings into specific pathologic conditions is unfortunately too common. Not only is this dangerous and unjustified, but it is often quite unnecessary if one would remember that there are usually additional ways of establishing the nature of the lesion. As an example, fibrosis or pneumonitis is too often postulated upon inadequate roentgen criteria, when



Fig 104 The primary tumor is located on the left but most of metastatic disease is found in the right side of the mediastinum Histologically this is oat cell cancer This form of lung neoplasm may present bulky disease resembling that seen in lymphosarcoma or Hodgkin's disease

a less restrictive opinion such as infiltrate, or consolidation, would be more accurate.

Diagnostic roentgenology when applied to cancer of the lung is subject to three distinct errors or faults The first and certainly the most tragic is the personal or individual error, almost always traceable to a lack of training and experience. Using the gauge mentioned before, *i e.*, the diagnostic standard established by what a majority of competent roentgenologists do under similar circumstances, it should then be possible for any physician to detect incompetence in a relatively short time.

The second fault may be called the acceptable or tolerable one. It may be typified by the presence of a one-inch well-demarcated homogeneous shadow of water density in the lung, the type to which the term "coin lesion" has been applied. While it might be possible to narrow the x-ray diagnosis somewhat by employing additional roentgen examinations of

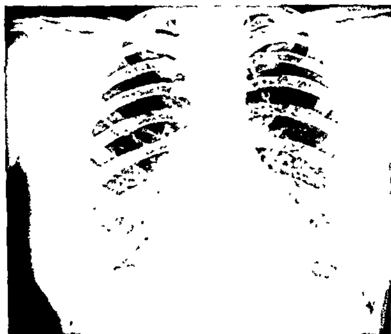


Fig 105 A small water density deposit is seen in the right lower lung field. This is an example of the so-called coin lesion. A precise x-ray diagnosis of the histology of these lesions is almost always impossible. This proved to be a terminal bronchiolar form of lung cancer.

the more time-consuming, costly, and dangerous varieties, there would be more willingness to accept any limitation of diagnosis that might go with the original study if it were known that the treatment required had already been clearly established. In no way would treatment be altered by the information that the additional examination might be likely to provide.

The third error is the inherent one, and it is basically a function of the size and the location of the tumor. Quite obviously there is a period of time between the development of the first cancer cells and the point at which the growing tumor can be detected by roentgenology. When the

equipment is modern, the technique perfect, and the lesion in an unobstructed area of the lung in a person of moderate size, the limits of detectability range from 2 mm. to 3 mm in diameter for a spherical water density process. But circumstances are not always ideal and practical detectability may be more often in the 3 mm. to 8 mm range. Even lesions of this size can be more or less hidden by ribs, heart shadow, diaphragm, and mediastinum. In chest survey work using smaller films,



Fig. 106. This is an example of the superior sulcus variety of bronchogenic carcinoma A water density mass is seen filling the apex of the left hemithorax. There is destruction of the posterior part of some of the upper ribs

the practical limits of detection are somewhat greater. Furthermore, large endobronchial lesions may not be discernible unless bronchography is done. We estimate that about 1 per cent of lung cancers fall within the inherent error and consequently are not detectable on the initial sagittal and lateral chest films.

The formulation of an x-ray report embodying a medical diagnosis is a more complicated procedure and a more serious responsibility than might be thought at first glance. The first roentgen examination of the chest, being a simple procedure, is usually ordered in a fairly standardized fashion. However, even at this stage the desires of the roentgenologist should be ascertained, for it is obvious that the one who is held responsible for an x-ray diagnosis must be given freedom to determine the technique of the study upon which his opinion must rest.

Therefore the *first* part of a report should evaluate, if need be, the

adequacy of the examination for the purpose it is expected to accomplish. There should be an evaluation of its technical quality as well, by mentioning any possible limitations. The *second* section of the report deals with detection, that is, whether the examination is negative or whether any abnormality has been found. The roentgenologist must hold himself personally responsible for the detection of any abnormality whatsoever that appears anywhere on the film or fluoroscopic screen The detection of a relatively minor change that might be curable lung cancer requires care, training, experience, and excellent technique It is at this point that the greatest chance for harm or good, as the case may be, can occur. *Third*, the report should offer a description or concise word picture of the lesion, so presented that the referring physician becomes acquainted with all the essential features of the disease. At times the roentgenologist can clarify the report by including a rubber stamp outline of a chest roentgenogram with the abnormalities drawn in. The *fourth* division of the x-ray report is the diagnosis Once in a while it may be justified to present an exact or histologic opinion. Usually, however, a single diagnosis cannot be made, but the lesion present can be placed into a disease category or grouping, a step which in itself may be sufficient to indicate the procedures that are needed or to point out the type of treatment that is to be followed. Occasionally there are accompanying lesions that also have to be evaluated as to their significance and importance. *Finally*, the report should indicate further roentgen studies that may be worthwhile This last point is often overlooked, but unless it is conscientiously carried out, the referring physician may be in doubt as to how to proceed

A final characteristic of good roentgen interpretation is the objectivity that stems from an open mind Particularly with diseases of the chest, the x-ray physician must realize that diagnostic roentgenology can stand on its own merits and that for the best interests of the patient it must be practiced as an independent specialty and not as part of any clinical work-up Therefore the examiner must always study the film or screen without prior knowledge of the clinical details, because it is only an unbiased mind that can be counted upon to produce consistent and reliable results After all, it is what can be read out of a film that is of value to the patient, not what can be read into it. Often no clinical information is needed to complete the x-ray report If it should be needed during a consultation or in the conclusion of the report as the situation may be, the roentgenologist may apply his specially slanted knowledge of disease in relation to its roentgen diagnosis, and seek pertinent and specific points of information

X-RAY ARMAMENTARIUM AND ITS EVALUATION IN THE DIAGNOSIS OF LUNG CANCER

The important criteria of competent roentgen diagnosis in cancer of the lung have been briefly discussed. Attention must now be given to the many different types of roentgen examination of the chest that are generally available today, as well as to the few that are just appearing



Fig 107A

on the horizon In carrying out this review an evaluation of the indications and potentialities of each different technique will be attempted so as to define its role in the diagnosis of lung cancer.

While the standard 14 x 17 inch sagittal film continues to be the foundation of the roentgen examination of the lungs, there is a growing appreciation of the value of a lateral view taken at the same time, especially for symptomatic patients. The necessity for reconstructing the living or three-dimensional relationships of a tumor from the single surface film with which the roentgenologist generally works is apparent, and the lateral view constitutes the simple procedure that usually makes this possible With modern techniques and equipment, it makes little practical difference which lateral is ordered, but generally one should try to see

that the diseased side is next to the film. Recommended technical factors consist of a rotating anode tube with 2 mm focal spot, film-focus distance of 72 inches and exposure time of $\frac{1}{20}$ sec along with all the other obvious earmarks of good roentgen technique A 200 ma. unit is usually the minimum capacity needed to provide complete roentgen coverage in chest diseases



Fig 107B

Fig 107A and B An uncommon histologic variety of lung cancer located in the root of the left lung It has produced no atelectasis in spite of its large size This is a malignant adenoma

Roentgenoscopy, which is usually the next logical step, occupies the same close relationship with the film coverage of the chest as exists in the gastrointestinal series Generally speaking, therefore, it is best done where facilities are available to procure any films that may be indicated This arrangement also insures a continuity of examiners and a singleness of responsibility Because the fluoroscopic examination is comparatively lacking in detail and is primarily suitable for depicting physiologic changes, it should not be used as a survey procedure, being considerably inferior in this regard even to the small photoroentgen film Another

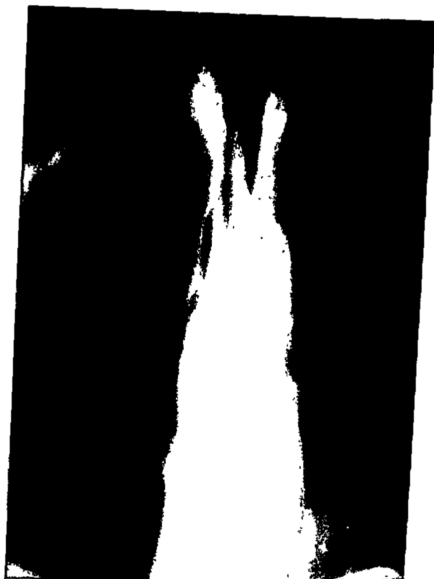


Fig 108 There is lung cancer located at the carina and extending into both right and left bronchi These bronchi display an irregular narrowing as seen on this tomograph Bronchography would have revealed the narrowing more clearly There was no atelectasis and the conventional chest film showed surprisingly little abnormality

objection to roentgenoscopy is the absence of a permanent record. We have found that when employed as an isolated form of examination, it is subject to a high percentage of false diagnoses, which to put it mildly can be disturbing and costly to the patient. Furthermore, recent surveys of fluoroscopes have demonstrated that a relative danger of overdosage exists because lack of training has led to utilization of outmoded, untested, and unsafe machines. Some of these units have revealed outputs of from 50 r to 100 r per minute, whereas an acceptable figure is from 10 r to 20 r. Because of circumstances such as these some writers have suggested that the use of fluoroscopes be licensed by the state. Certainly until more is known about the late effects of radiation upon human beings all exposure must be kept at a minimum. Who can say, however, regarding the employment of the fluoroscope as an isolated diagnostic tool, that the dangers of an incorrect diagnosis may not far outweigh those of radiation overexposure?

Roentgenoscopy of the chest should follow a scheme in which all pertinent areas within the thorax receive adequate attention as part of a routine. After careful scrutiny of the tumor and its neighborhood, the different organs and anatomic divisions of the chest are observed. Then the various functional characteristics of the diaphragm, vocal cords, lung roots, esophagus, and heart and great vessels are examined more or less in the order named. As each area or organ is studied, the special tests that have been developed for its evaluation are applied. The esophagus should be opacified in chest fluoroscopy because of the ability to reveal unsuspected abnormalities such as masses deep in the mediastinum. We have known of two cases in which the failure to carry this out has led to a spurious surgical attack upon a dilated esophagus due to cardiospasm, on the erroneous impression that the right-sided mediastinal shadow was a solid tumor. One of these cases had angiocardiographic studies! Serious mistakes such as this can be avoided by adopting a sensible fluoroscopic program and carrying it out.

The fluoroscopic image amplifier, now coming into clinical use, somewhat extends and broadens roentgenoscopy. It is part of our equipment and at this time certain opinions concerning it seem justified. The image amplifier is still rather expensive and quite bulky, and the screen area is limited in size. However, the attachment does bring several advantages to roentgenology. It permits fluoroscopy with little or no accommodation in a room where only slightly reduced lighting is needed. This is of greatest advantage for teaching or when roentgenoscopy is used in conjunction with different manual procedures requiring good illumination throughout the room. These include for example, bronchography, sinus tract injections, cholangiography, and catheterization of the vessels. Another advantage is that the amount of x-ray exposure to the patient often



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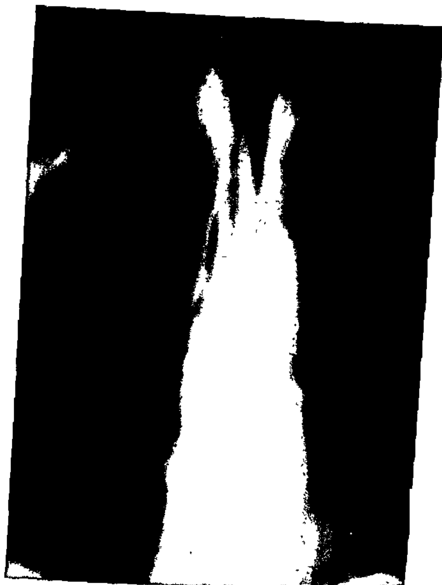


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in teaching and in the combined type of fluoroscopic procedure, and some improvement in visibility would seem to summarize its status at this time, but new developments in design may follow.

Following roentgenoscopy the x-ray physician has available a wide range of special studies at his command Judicious selection of the simplest films that will answer a point of information is the earmark of the astute examiner, because these different examinations provide a test for the ingenuity of the roentgenologist who, by selecting from the different techniques and positions available, can custom-fit an x-ray visit to the situation at hand A careful consideration of these special film studies is now indicated.

Stereoscopic 14 x 17 inch sagittal and sometimes stereoscopic lateral chest films are particularly valuable when searching for tiny lung densities such as metastases For providing a more thorough understanding of the detailed relationships of a lesion in respect both to its internal pattern and its association with normal structures, stereoscopy is unsurpassed The possibility of dependably localizing tiny lung densities anatomically as to lobe or segment should not be overlooked, because at times it may be difficult or impossible to do so because of failure to see an opacity in both single sagittal and lateral views In this regard stereoscopy is usually cheaper, simpler, and quicker than tomography The technique of the stereoscopic x-ray examination is basically the same as given for the single chest film, but the procedure is a little more demanding on the part of the patient as to body immobilization and control of respiration

The expiratory film provides a simple and at times uniquely informative x-ray method of examining the chest It is employed most advantageously to demonstrate minor degrees of pneumothorax, to reveal areas of obstructive emphysema, and to record the relative aeration of the lungs A comparison with the conventional or inspiration film will help to bring out most clearly any slight degree of aeration change that is present An expiration-inspiration film series is a much more sensitive and reliable indicator of most aeration abnormalities than fluoroscopy, and the same reliability holds true for determining mediastinal shift or abnormal mediastinal movement In regard to any mediastinal change of position occurring in lung cancer, the lesion causing the displacement is usually obvious, the mediastinal disturbance being of secondary importance.

Another special film examination of occasional usefulness is the apical or lordotic view designed to reveal the upper lung fields largely cleared of the disturbing shadows of ribs and clavicles While it is indicated more often in the minimal lesions of pulmonary tuberculosis, the apical view can be very helpful in revealing small tumors, particularly those of the superior sulcus variety.

can be cut appreciably. Fluoroscopy done in the conventional way with well-calibrated equipment employing adequate filtration and a timer should offer little if any possibility of over-dosage or danger to the patient or the examiner, but any piece of equipment that will diminish



Fig 109 This is a spot film taken during a bronchographic study on a patient with lung cancer, showing an area of atelectasis in the right upper lobe with filling of the bronchus to one upper lobe segment, but with absent and partial filling of the two remaining upper lobe bronchi

the radiation delivered to a patient has an advantage. A further aspect of image amplification is that under many conditions there is some improvement in fluoroscopic detail. As it now exists, the image amplifier will probably bring about few fundamental changes in the principles of fluoroscopy that have been built up over the years, nor can one foresee any far-reaching improvement in the x-ray diagnosis of lung cancers through its use Some broadening of fluoroscopic facilities, especially

In this circumstance it is preferable to do a localized type of bronchial opacification by means of a catheter introduced through the larynx. The tip of the tube is manipulated fluoroscopically to the region of the bronchus under question. A small amount of opaque material (5 to 10 cc) carefully injected under roentgenoscopic vision and manipulated by proper positioning of the patient will usually provide adequate visualization of the bronchial portion of the lesion. Spot films of the lesion taken while fluoroscoping, are often most rewarding. The successful completion of controlled bronchography requires a good prior knowledge of the lung lesion and prompt roentgenographic coverage of the opaque liquid as it outlines the affected bronchus. Otherwise delay of a few minutes can cause diffusion of the material.

The survey form of bronchography on the other hand is less often indicated in lung tumor work. In this method the radiopaque liquid is introduced by gravity across the larynx in various ways, such as by running it over the back of the protruded tongue. Selected areas of the lungs and their bronchial branches are visualized by proper positioning of the patient. Wide regions of the lung are depicted and adjacent segments are often needlessly filled. Film coverage under these circumstances depends more on conventional than on spot films, with stereoscopic sagittal and single obliques as the standard if both lungs are opacified.

Two groups of bronchographic opaques are available. One, the iodized oils, have been in use for many years. They are generally easy to work with, having a most satisfactory density and a low degree of irritability in the tracheobronchial tree. Their greatest disadvantage is that they tend to remain in the lung, particularly in diseased areas, for days or months, effectively obscuring findings of importance on subsequent films. It is becoming evident also that these oils are not quite as innocuous as had been believed, for a few instances of adverse reactions have been noted. If there is a good chance that the lung will be removed promptly, retention of the material is no drawback.

The second group of bronchographic opaques, the water-soluble ones, have been introduced more recently. These are thought to be more difficult to work with because they seem to be more irritating to the bronchial surfaces and certain of these materials can lose their density quite rapidly. On subsequent chest films in a day or so all roentgen film traces of these agents will have disappeared. In our x-ray department the iodized oils are used much more frequently than the water-soluble opaques, both being equally available to the roentgenologists who do this work.

Tomography, planigraphy, sectional roentgenography, or whatever other designation one prefers, is another kind of x-ray techniq occasionally provide helpful information about

Occasionally a small "spot" film taken with a special cone and with appropriate alteration of conventional techniques may provide better detail for bone in a selected area A different type of small film taken on the spot-filming device during fluoroscopy may also be of value in bringing out certain special relationships of a tumor.

Films taken with a moving grid by means of the Potter-Bucky diaphragm are frequently necessary in lung cancer because they provide the best way to show the bones in detail. Another purpose of moving grid films is to penetrate through superimposed densities to demonstrate cavities, fluid levels, calcium deposits, or the structural details and texture of a bulky lesion. Needless to say these attributes make moving grid technique a frequent requirement.

Decubitus films, in which the moving grid is generally used, may be needed in the roentgen evaluation of lung cancer and its complications This examination can be done in either right or left lateral recumbency or erect position and even an inverted placement of the patient has been employed. Decubitus, erect, and inverted films help to establish the presence, location, and size of fluid accumulations They may detect the occurrence and show the extent of any loculation. Decubitus and other special position examinations can show the size and the contour of the inner border of cavities An additional indication is to displace pleural fluid away from the areas in the lung that one wishes to visualize. At times very small amounts of fluid may be detected by this method and a differentiation may be possible between pleural thickening and fluid Mediastinal mobility can also be tested.

Kymography deserves little if any mention in the x-ray investigation of lung neoplasms It is of potential value in the differential diagnosis of masses lying adjacent to or within the mediastinum, but employment of the simpler x-ray procedures usually will make kymography needless. Moreover, contrast visualization of the vascular system offers much more than kymography in this respect.

Bronchography properly conceived and executed may provide information not otherwise obtainable about lung cancer. In the evaluation of the bleeding lung, at a time when preliminary x-rays may be negative, bronchography may reveal an unsuspected bronchiectasis or small endobronchial tumor Bronchography is the most reliable x-ray method to show the condition of the bronchi, usually surpassing tomography. Sometimes false impressions can be due to air droplets and retained secretions, or acute bending and compression of the airway resembling an intrinsic endobronchial lesion.

Bronchography is planned along two general lines depending upon the object to be attained. Usually when the tentative diagnosis is lung cancer, interest lies in a single bronchus and the area of the lung it supplies

already gained by other x-ray examinations with what one wishes to accomplish by the body section study The best position for the patient, the depth and number of the tomographic cuts, the thickness of the sections, the exposure factors, the control of respiration, all these and other items have to be decided upon beforehand Transectional roentgenology in which the cuts are made horizontally while the patient is erect is an interesting variation in body section roentgenography, but not one of great practical significance for lung cancer

What then are the indications for sectional roentgenology particularly as concerns lung cancer? In general these may be largely of a confirmatory nature. First, when cavitation is suspected within a dense area, it may be substantiated by this method Usually, however, it can be adequately shown by simpler means such as stereoscopy alone or combined with moving grid techniques Sometimes it is important to be sure of the presence of calcification within a lesion and also to know something of its arrangement or pattern Generally this can be established satisfactorily by other means So far we have not seen calcification revealed by tomography that could not have been either suspected or diagnosed by simpler films Sectional roentgenography has been employed by some to survey the lungs for tiny nodular metastases not thought to be demonstrable by other means. We have not yet seen a water density deposit in the lung that could not also have been revealed by some other form of film examination On the other hand there have certainly been a few occasions in which tomographic survey of the lungs showed a deposit or two that were not seen on a sagittal P A stereo of the chest because of superimposition of mediastinal structures However, with lateral stereos these deposits would probably have been demonstrated At present therefore it is felt that while tomographic survey has an added use in seeking small lesions such as metastases, it should be done sparingly and only after conventional films, particularly stereoscopic ones, are negative When dealing with small densities chance plays an important part

Finally, tomography can show certain features of the aorta, large pulmonary veins, lung roots, and other vessels, but these vascular structures of the chest are best shown by opacification methods, at least as far as their application to the diagnosis of lung cancer is concerned All the finer details and many of the normal relationships of conventional roentgenology are not seen on tomography, so that often the apparent clarity with which some shadows appear may be misleading Too often have we seen a blood vessel diagnosed as a metastasis, blebs or bullae called cavities, an area of normal lung surrounded by patches of pneumonia called lung abscess, and even the rhomboid fossa of the clavicle called a bone metastasis! It would seem to be a sound principle that no

procedure, which employs anything from a simple mechanical attachment on a conventional x-ray machine to a complex, specially designed unit, a selective visualization in a thin section, sheet, or plane of the body is



Fig 110 Angiocardiogram on a patient with lung cancer of the left upper lobe involving the chest wall, showing venous obstruction leading to the filling of neighboring veins

made possible by a smudging or blurring action on the x-ray images of neighboring structures that would otherwise be superimposed. Beyond this ability to "see through" superimposed material, it can do no more than other types of roentgenography because the detection of a lesion is possible in roentgenology only insofar as density differences exist between the lesion and its surroundings. Every tomographic examination requires good planning, based upon a careful correlation of the findings

ment, the situation is further complicated Contrast studies can be of great help in demonstrating the nature and extent of the vascular lesion in patients with mediastinal obstructive phenomena, although a broad localization can often be done quite well clinically. One should be particularly careful in doing angiography on patients with venous obstruction because of the increased possibility of their developing a thrombophlebitis A less concentrated opaque solution should be used with these patients. The occasional death resulting from angiocardiography should also warn that not only must the contraindications to its application be carefully observed, but it should be used only when there is a fair chance of its accomplishing worthwhile results.

An induced pneumothorax is justifiable as a diagnostic procedure in the roentgen diagnosis of lung tumors on rare occasions because it may be a definite means of establishing that the lesion is either pleural, pulmonary, mediastinal, diaphragmatic, or cardiac in location Generally speaking, its chief indication would seem to be in differentiating between a surgical disease such as tumor and a nonsurgical one like herniation or eventration Masses on the liver surface or localized hernias can cause a shadow at the lung base difficult to diagnose precisely by x-ray unless pneumothorax was done A diagnostic pneumoperitoneum combined with the pneumothorax would provide clear identification of both diaphragm surfaces and rarely this may be the only way, short of surgery, to tell from where a mass lesion arises Fortunately, the normal gas bubble in the stomach makes this side of the diaphragm easier to evaluate by roentgenology than the right Retrorectal pneumography is an alternative to consider instead of pneumoperitoneum, as a way to reveal the abdominal surface of the diaphragm The addition of special film procedures such as stereoscopy, decubitus films, and sectional roentgenography are called on to make the different gas injection studies more productive

If it is indicated, aspiration biopsy of a lung lesion can be carried out, but always under roentgenoscopic guidance and after careful planning of the approach based on previous films and fluoroscopic findings Where there is reliable evidence of non-resectability of a lung lesion but it is still

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be secured after an aspiration biopsy to determine whether a pneumothorax has developed

There are several newer developments in diagnostic roentgenology of the chest that have a possible significance for lung cancer. One of these is the employment of higher kilovoltages in the making of chest films, i e, in the range from 100 to 150 kv Somewhat special x-ray equipment

process should be finally diagnosed on the basis of a tomographic examination alone

Contrast visualization of the heart and great vessels by the injection of a bolus of radiopaque material such as iodopyracet occasionally enjoys a place of some consequence in the roentgen work-up of lung cancers However, to say as some have that it should be a part of the routine work-up of patients suspected of having primary lung cancer indicates a high degree of overemphasis and attests to a failure to integrate roentgen diagnosis with clinical management. It should be apparent that the need for angiocardiography depends considerably on the role given to surgery in the handling of malignant new growths of the lung. When the thoracic surgeon is most radical in his approach, there is less need for contrast visualization, but when he is less aggressive, contrast visualization is more often justified. In general, conditions other than blood vessel involvement generally constitute the basis for non-resectability. Satisfactory visualization of the lung vessels can be done with standard office equipment, but when heart chambers or specific areas of the great vessels are to be shown, some method of obtaining a rapid sequence of films is generally required

Angiocardiography may serve three general purposes in cases of suspected lung cancer. First, it may further the diagnosis Second, after the diagnosis of tumor seems secure, it may aid in defining its localization and extent. Lastly, it may reveal more precisely the effect the mass has on the vessels.

Contrast visualization may establish whether or not the lesion is a vascular anomaly of the lung vessels, or it may be needed to settle the nature of a mediastinal or juxtamediastinal density if there is any possibility of aneurysm These problems can often be decided by simpler x-ray means Everyone has come to realize that all primary tumors of the lung should be treated by resection if possible. It follows therefore that the only reliable way to differentiate between a benign and a malignant process is to obtain histologic proof Hence x-ray findings in the lung vessels suggesting that a lesion is benign, such as gentle displacement without narrowing, irregularity, or "staining" of the tumor bed by the opaque liquid, not only can have no practical application, but have yet to be proved dependable. There is no way by which an assurance that lung tumor is benign can be made angiocardiographically

Marked displacement of a great vessel, narrowing, complete obstruction and actual vessel invasion by tumor, one or more of these may support an opinion of non-resectability In our experience however it has not been regularly possible to distinguish between a narrowed vessel due to compression and one having intrinsic tumor invasion. With thrombosis and embolization giving x-ray findings similar to those of tumor involve-

ment, the situation is further complicated Contrast studies can be of great help in demonstrating the nature and extent of the vascular lesion in patients with mediastinal obstructive phenomena, although a broad localization can often be done quite well clinically One should be particularly careful in doing angiography on patients with venous obstruction because of the increased possibility of their developing a thrombophlebitis A less concentrated opaque solution should be used with these patients The occasional death resulting from angiocardiography should also warn that not only must the contraindications to its application be carefully observed, but it should be used only when there is a fair chance of its accomplishing worthwhile results

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If it is indicated, aspiration biopsy of a lung lesion can be carried out, but always under roentgenoscopic guidance and after careful planning of the approach based on previous films and fluoroscopic findings Where there is reliable evidence of non-resectability of a lung lesion but it is still important to obtain a histologic diagnosis before embarking on a course of radiation therapy, it would seem justifiable to try an aspiration biopsy, especially if the radiation therapy can be planned in a way that it will include the route of the needle A postoperative chest film should always be secured after an aspiration biopsy to determine whether a pneumothorax has developed

[illegible]

i e, in the range from 100 to 150 kv Somewhat special x-ray equipment

and additional protection problems are entailed. The method has now been tried sufficiently long to permit it to be fairly reliably estimated. The technique provides a film with less contrast but one in which there is less masking effect by bone and mediastinal structures to whatever small deposits might be present. That it really accomplishes sufficiently more than good technique with conventional methods is debatable. While quite widely employed at this time, it is by no means universally accepted.

With the recent manufacture of a 0.3 mm. focal spot x-ray tube, it seems possible to demonstrate small selected areas of the lung in a little greater detail. Perhaps some of the lung lesions will permit magnification with this technique and it may be possible to extend one's ability to judge calcification. As yet we have had no personal experience along these lines, but it would seem worthwhile to investigate the interesting possibilities of this new technique.

A third innovation is based upon the use of voltages in the range of one to two million. Consequently it employs x-ray therapy apparatus which is not really suited for diagnostic purposes. Its advocates feel that it may offer some advantages in survey work of the chest because the obstructive effect of the bones and the mediastinum is largely overcome in this voltage range. At this time however the long exposure required and the large focal spot cause blurring with loss of detail, and an increased amount of radiation exposure to the patient. These, along with the expensive equipment and its poor design for diagnostic purposes, place this method definitely in the experimental stage.

No discussion of the armamentarium of diagnostic roentgenology in lung cancer can be considered as thorough without a consideration of photoroentgen chest surveys. While originally conceived as a means of finding tuberculosis, and as yet still receiving their main stimulus from this function, x-ray surveys of the chest are revealing a certain number of unsuspected and sometimes curable lung neoplasms. Whether they can be justifiably employed to find lung cancer in a known nontuberculous segment of the population remains to be determined. It is hoped that an answer to this problem will be forthcoming as our chest survey program is continued. A number of physicians and surgeons have advocated such a procedure but one suspects their idea is often based more upon good intention than on a thorough personal experience with chest surveys.

The Department of X-ray Diagnosis at the Memorial Center for Cancer and Allied Diseases has just compiled its findings in a chest survey totaling 100,000 examinations and covering a period from 1947 to 1952. The ... of asympto-
... clinic,
... yee ranks,
the outpatient department of the hospital, and ...

were presumably themselves specially interested in cancer and therefore were considered to be more amenable to recommendations for diagnosis and treatment once a lesion was discovered, than would a random group. The entire hospital staff is of course primarily oriented to the detection and management of neoplasms. The x-ray department arranged for all chest survey films (4 x 5 inches) to be read independently by two roentgenologists and for the opinions on questionable cases to be correlated by a senior staff member Often a comparison with chest photoroentgens taken in preceding years was possible About 20 per cent of patients returned for yearly studies

The ages ranged from 5 to 84 with most patients falling into the 40- to 44-year column. Ages dropped equally on both sides of this peak Obviously this is too young an age distribution to be ideal for lung cancer detection Females outnumbered males about three to two Out of the total of 100,000 persons examined, 24 unsuspected primary cancers of the lung were proved histologically Seventeen of these were totally asymptomatic, seven had symptoms which, though mild, were nevertheless significant as viewed in retrospect In fairness, it must be stated that in some of the seven symptomatic patients their complaints were so slight that they would readily escape the routine questioning as conducted in a busy cancer detection clinic Seven of the 17 asymptomatic lung cancers were resected, six were non-resectable and three were non-operable One refused surgery In the seven symptomatic cancers one was resectable and three were not, two patients were not operable, and the final patient was lost to follow-up No five-year cure has appeared as yet The tuberculosis cases discovered were catalogued as 271 presumably stable, 430 potentially significant tuberculous lesions, and 18 significant and proved cases of pulmonary tuberculosis. The 430 potentially significant cases are undergoing additional evaluation. Apart from the tuberculosis and lung cancer case-finding that the survey accomplished, an interesting recovery of other diseases was brought to light. There were 14 lesions proved at operation consisting of four tuberculomas, four hamartomas, and one each of the following bronchial adenoma, lung abscess, dermoid tumor, lipoma, bronchogenic cyst, and herniation through the foramen of Morgagni There were eight potentially significant bone lesions that were not proved histologically but which were probably fibrous dysplasia and enchondroma Five bone lesions that were proved histologically included three cases of fibrous dysplasia, one nonosteogenic fibroma, one multiple myeloma, and one osteogenic sarcoma which is now living with no evidence of disease following resection Two cases of unsuspected metastatic cancer in the lungs were also revealed

One discouraging feature brought out in this analysis was the occa-

sional error in film interpretation committed even though independent double reading, good techniques, and trained x-ray personnel were employed. There was an unexpectedly high degree of patient resistance to the recommended steps of diagnosis and treatment. Surprising to us also was a certain disinterest on the part of some physicians to recommendations by the roentgenologist for further studies to confirm and diagnose the lesion once it was detected by the survey. Patient resistance and physician disinterest together were responsible for a loss of follow-up on 69 out of 107 possibly significant tumor-like abnormalities brought to light by the photoroentgen survey. There was often a serious time lag before definitive treatment. The advanced stage of some asymptomatic lung cancers is always disheartening. In general it must be said that the accomplishments of the project as regards cancer of the lung, while somewhat less than might have been attained, showed a higher detection rate than has usually been reported in chest surveys.

As much as one dislikes relating human life to money, there seems to be so much need for the medical dollar that some balance must be kept in fairness to all. Furthermore, one knows that our economy cannot justify survey expenditures beyond a certain point. While it is of course impossible to get an exact cost figure, as nearly as we can determine the amount of money required to bring a resectable cancer of the lung to operation was about $5000. Such a figure neglects the very real contribution of the discovery of other significant disease, particularly tuberculosis, but the amount has real value in establishing the cost of finding potentially curable lung cancer. These findings as well as those reported by others indicate that a thoroughgoing revision of most chest surveys including the present one is needed before they can be recommended solely as a lung cancer-finding procedure. First there must be film interpretation by mature roentgenologists especially interested and experienced in lung cancer. Independent double readings seem necessary. All possible technical improvements in survey filming must be utilized. Then there should be some way to impress upon patients before they are accepted in a survey that they are obligated for their own welfare to follow promptly the recommendations that are given them if a lesion should be found. It also seems advisable to develop a special team of chest internist, pathologist, thoracic surgeon, and diagnostic roentgenologist to whom the diagnosis and treatment of suspicious lesions will be entrusted. Besides all this an efficient organization, be it based upon a detection center, outpatient department, or social service, is required to carry out the necessary patient contacts and bookkeeping. If a survey for lung cancer alone were to be conducted, then certain limitations regarding the people to be surveyed would be indicated. The age should be closely restricted to parallel that of the high incidence of

lung cancer The survey should be directed primarily to the male population and apparently it should also include the heavy cigarette smokers.

THE FORMULATION OF A ROENTGEN DIAGNOSIS OF LUNG CANCER

Outline of Roentgen Diagnosis of Lung Cancer

I. The roentgen characteristics of the primary mass
  A Appearance
    1. Location
      a Bronchial
        (1) endobronchial
        (2) exobronchial
        (3) combined
      b Pulmonary
        (1) chest wall
        (2) juxtamediastinal
        (3) lung root
        (4) diaphragm
        (5) superior sulcus
        (6) central
    2 Shape
      a Endobronchial
        (1) spherical
        (2) plaque
        (3) annular
      b Exobronchial
        (1) spherical
    3 Size
    4 Borders
    5. Texture and density
      a average
      b calcification
      c abscess
  B. Effects due to pressure and or invasion
    1 Bronchus
      a obstruction partial, complete, ball-valve
        (1) atelectasis
        (2) emphysema
        (3) infection
    2 Vessels
      a displacement
      b narrowing

THE FORMULATION OF A ROENTGEN DIAGNOSIS OF LUNG CANCER (Continued)

c. obstruction
d. invasion
3. Nerves
a. paralysis
(1) recurrent laryngeal
(2) phrenic
4. Pericardium
5. Heart
6. Esophagus
7. Bones
8. Chest wall
9. Pleura
10. Diaphragm

II. Roentgen characteristics of metastases
A. The metastases within the thorax
1. Appearance
a. number
b. location
c. shape
d. size
e. borders
f. texture and density
2. Effects due to pressure and/or invasion
a. bronchus
b. vessels
c. nerves
d. pericardium
e. heart
f. esophagus
g. bones
h. chest wall
i. pleura
j. diaphragm
k. lungs
B. The metastases outside the thorax
1. appearance
2. effects
3. special clinical states

III. The development and course of lung cancer
A. Growth rate
B. Treatment effects

There are three possible morphologic changes that may take place in a tissue or organ These are loss of substance or ulceration, replacement by abnormal material or infiltration, and overgrowth or formation of a mass It is this last change that is of paramount significance in the roentgen diagnosis of lung cancer because it constitutes the basic diagnostic unit. The mass due to lung cancer has two general categories of x-ray findings that must be evaluated The first is appearance, which is composed of size, shape, borders, texture, density, and location, and the second is the effects produced by the mass upon the different structures within the chest. The possible effects are two, that of pressure leading to displacement or compression, and that of invasion or growth into neighboring tissues The structures upon which these actions may be demonstrated roentgenologically are vessels, nerves, bronchi, heart, pericardium, esophagus, chest wall, bones, pleura, diaphragm, and the lung itself

In addition to the x-ray findings due to the primary tumor mass, a second group of changes stems from the metastases The appearance of any metastatic deposit and the effects it produces are considered in the same order as those outlined for the primary tumor The examiner deals first with the metastases in the chest, such as those in the lung root, mediastinum, opposite lung, bones, or pleura, and secondly he evaluates those deposits that occur elsewhere in the body

Finally, the information that has been obtained by this systematic analysis must then be related to the known life history of lung cancer, its duration, growth rate, expected complications, and the effect of any treatment that may have been given To do this satisfactorily the roentgenologist needs a thorough knowledge of the development and course not only of lung cancer but of the other diseases that can produce similar roentgen manifestations

There will be many occasions when it will not be possible to judge each diagnostic point fully because of masking by such conditions as fluid, pneumonia, atelectasis, or the very bulk of the primary or secondary masses of tumor However, it is often gratifying to note to what degree individual findings can be identified by a careful analysis of the roentgen films This approach to the roentgen diagnosis of lung cancer has the advantage that it tends to reflect the actual changes occurring during the progress of the disease

The primary tumor in its early stage may be located either entirely within a bronchus, completely outside the bronchus, or, as is more often the situation by the time the cancer becomes symptomatic, both endobronchial and exobronchial components may be present All primary tumor masses detectable by conventional films must involve the lung substance to some extent Because lung cancers may occur anywhere along the bronchial tree or wherever there is lung substance, we doubt

that there is much practical value for roent- [illegible]
that most lun- [illegible]
eral parts [illegible] genologist must assume responsibility fo[illegible] discovery of any cancer in any location provided it falls within the range of detectability. In this connection it is important to know that there are certain relatively blind areas of conventional roentgen films that deserve special scrutiny. Small lesions in the juxtamediastinal position in either lung, particularly at the manubrial level anteriorly where the two lungs can be in apposition, may not be seen without a lateral view. The retrocardiac areas are other relatively blind spots of the single sagittal chest film A small tumor in the extreme apex of the lung may also be difficult to identify. Then again densities that are located posteriorly at the lung bases may be obscured in the single sagittal film by the curve of the diaphragm The masking effects of the bones have been mentioned. Small deposits in lung substance adjacent to the lung roots can be particularly difficult to recognize although an intimate knowledge of the normal roentgen pattern of the hilus will make such problems less frequent.

The customary density of lung cancer roentgenographically is that of water, the same as that of the vessels, pleura, diaphragm, all body fluids, and all other solid organs except the bones. The texture or structural pattern of a lung cancer can vary rather considerably, but this variation occurs usually only after it has attained considerable size. Tiny lung cancers are regularly homogeneous and structureless, having no pattern or texture Some of the changes that may take place in the structure of the lung cancer can be used as an aid in its recognition Once in a wh[illegible] the cancer may be [illegible]
There may occur [illegible]
presence of locali[illegible] [illegible]ysema.

Necrosis is one complication that may markedly affect the internal pattern of the original tumor when it is followed by liquefaction and emptying through a bronchus Certain roentgen points have been marshaled regarding the differential diagnosis of a pyogenic abscess and one due to necrosis of a malignant tumor While these are of some interest to the roentgenologist, they are not of great practical impo[illegible] be-
cause one [illegible]
tion to rul[illegible]
abscess oft[illegible] [illegible] that give a strong clue to its deadly nature, this is not always the case There is no way that the examiner can be absolutely certain of the diagnosis of a solitary pyogenic abscess on a single roentgen examination. Abscess formation may occasionally be multiple in a tumor, but these are confluent, whereas multiple separate lung abscesses are almost always inflammatory.

Another way for the usual homogeneous texture of lung cancer to be altered is by calcification. There is no reason why a lung carcinoma may not develop at the site of an existing calcification in the lung and, by growth, associate the calcium deposit with the tumor. Furthermore, in the later stages of tumor growth it would seem theoretically possible for calcification to develop in the tumor itself, because any area that may necrose may in time calcify. It is believed therefore that the mere presence of calcification within a mass is not sufficient evidence to exclude completely the possibility of cancer. However, a more searching study of the calcification might reveal characteristics by which cancer could be excluded. For instance, if the calcific deposit were single, centrally placed, relatively large, and located within a spherical water density mass with distinct border, and especially if the calcification were deposited in concentric rings, then it is believed that tuberculoma could be diagnosed and cancer effectively ruled out.

Occasionally the primary mass can present clearly defined edges, so distinct that a cystic lesion may be suggested. Oat cell cancer tends to do this. On the other hand the margin may be quite irregular and ill-defined with an appearance resembling pneumonia or a patch of tuberculosis. Squamous carcinoma and terminal bronchiolar carcinoma may look this way. Usually, however, the periphery is fairly distinct in most lung cancers. Nevertheless, experience indicates that the border is subject to such variation that it generally has little to do with the roentgen identification of a lesion as lung cancer.

The shape of lung cancer is spherical in almost every instance by the time it first becomes visible roentgenologically. This spherical shape may remain as the tumor develops or it may undergo certain modifications. For example the cancer can assume the configuration of a segment or even that of a lobe. When the tumor reaches a pleural surface, it tends to present a flattened aspect along that border. If the neoplasm is endobronchial, the different shapes that it may assume are either spherical, an elevated plaque, or an annular defect of variable length surrounding and narrowing the bronchial channel. The spherical tumor will appear as a circular filling defect of water density in an otherwise normal bronchial tube if bronchography or tomography is done. Sometimes, as in the trachea or large bronchi, the surface of an intraluminal mass can be demonstrated in double contrast by means of a thin layer of opaque coating. A bronchial narrowing, whether symmetrical or asymmetrical, smooth or irregular, may be due to a completely endobronchial tumor, but it can also be caused by extrinsic pressure on the bronchus and by bronchial invasion from without. One possible clue to the origin of the narrowing would be x-ray evidence of bulky disease outside the constricted airway. Generally speaking, however, there is usually little in

the shape of the bronchial constriction that is specific for an x-ray diagnosis of cancer. For instance, the narrowing associated with other forms of atelectasis cannot be distinguished regularly from that caused by a lung cancer in which the configuration of the shut-off may be abrupt or fusiform, smooth or irregular, straight or curved. Of all these, separately and in their various combinations, it is only when the obstruction is abrupt with a spherical or convex intralumenal defect that tumor is rather definite.

The effects brought about by the primary may be complicated and varied. Fundamentally these are either *pressure or invasion changes*, and of course it is not possible in all circumstances to distinguish roentgenologically between the two Fortunately it is not necessarily important that such a distinction be made.

The conditions that a cancer may bring about because of bronchial obstruction are of particular interest to the roentgenologist because they occur so regularly that their presence aids materially in diagnosis. The tumor *may cause either partial, complete, or an intermittent bronchial* obstruction, the latter constituting at times a so-called ball-valve phenomenon. Bronchial occlusion may bring about various conditions distally such as atelectasis, emphysema, and infection as well as combinations of each of these. If the bronchial obstruction shifts in location, so too will the changes that are based upon the narrowing. *The shifting* nature of these findings is in itself an important piece of roentgen evidence for lung cancer

There is often nothing particularly suggestive about the atelectasis due to lung cancer The collapse may be lobular, subsegmental, segmental, or lobar, or it may even involve the entire lung A thorough knowledge of the roentgen diagnosis of atelectasis is of course a prerequisite, but besides this certain aspects having special significance for the roentgen diagnosis of lung cancer need emphasis Many times it is possible to *distinguish the presence of the tumor mass itself from the accompanying* atelectasis by the presence of a bulging or localized enlargement of the shadow due to the collapse. Furthermore, because there is so often accompanying disease of one form or another within the vicinity of the atelectasis, one must not always expect to see the typical roentgen picture of collapsed lung The presence of fluid, infection, or, as we have mentioned, the tumor mass itself, may hide the more striking roentgen *features, and consequently one must* depend upon the secondary signs of atelectasis, such as a change in the normal position of the lung root, displacement of a fissure, or failure of the mediastinum to be displaced in the presence of pleural fluid

Obstructive emphysema due to lung cancer may have a distribution similar to that of atelectasis *Emphysema that is due to bronchial ob-*

struction is best demonstrated by a comparison of inspiration and expiration films, the essential findings being an increase over the normal in the volume of an area accompanied by a diminution in the number of its blood vessels per unit field as compared with the normal lung. It is important that there be a distinction between the localized obstructive emphysema and that of either a compensatory or generalized form, as the diagnostic implications are quite different. With the more extensive degrees of obstructive emphysema, mediastinal shift with respiration and limitation of diaphragmatic motion on that side may also be detected.

Just as in the case of atelectasis or emphysema it may be that the infection following a bronchial obstruction is more evident roentgenologically than the tumor that causes the bronchial effect. Infection may take the form of a patch of segmental pneumonia, areas of bronchopneumonia, bronchiectasis, abscess—either single or multiple, or combinations of these conditions. Usually the distribution of the infection will correspond to the bronchus involved. If there is anything atypical about a lung infection either clinically or in its roentgen appearance, such as a tendency to persist unduly or to recur, then prompt steps are indicated to try to determine whether there is any underlying tumor.

One or more of the great vessels of the mediastinum or of the lung may be either displaced or narrowed by the pressure effect of a tumor, or they may be invaded to the point of partial or complete obstruction. By means of angiocardiography the presence of either of these two effects can usually be detected. Of the different alterations of this nature that may be seen, the occlusion of either the left pulmonary artery near its origin, or of the right pulmonary artery proximal to its bifurcation, have been used as contraindications to resective surgery. Changes of the same type in the great veins of the mediastinum usually hold similar significance. Angiocardiography may also help to determine if there is involvement of the heart and the pericardium by tumor. Sometimes a puzzling density in the lung root may be clarified by this procedure.

Involvement of two important nerves, the recurrent laryngeal and the phrenic, may be detected roentgenologically. It may not be widely appreciated that the vocal cords can be studied roentgenoscopically, and that recognition of vocal cord paralysis is possible, although not with the degree of dependability made possible by mirror or endoscope. Fully developed diaphragmatic paralysis is readily evident, but for partial or minor degrees, special tests are indicated. Having the patient sniff is one of the best of these, because it throws a sudden severe load on the diaphragm, thereby bringing out minor limitations of function not otherwise detectable. The clinical and radiologic implications of nerve involvement are not always obvious because a paralysis might be due to an unrelated condition or may have been present previous to the presence

of the tumor There are instances of five-year survivals following resection when a nerve paralysis had been present.

Invasion of the pericardium and the heart by neoplasms of the chest is not infrequent. Generally speaking there are other more dependable ways of detecting heart and pericardial involvement than by means of routine x-ray studies. However, detection of a mass of tumor disease adjacent to the heart, an enlargement of the heart silhouette taking place during a relatively short period of observation, and the presence of an abnormal cardiac contour along with fluoroscopic evidence of alteration in the function of the heart and great vessels, are suggestive of tumor invasion. If it seems worthwhile clinically, then opacification studies of the heart and great vessels may be more revealing and informative. While there are many roentgen signs that suggest a pericardial effusion, use of angiocardiographic methods permits an unequivocal roentgen diagnosis of this condition.

The esophagus lends itself particularly well to roentgen evaluation as to whether it is pressed upon, displaced, narrowed, or invaded by tumor. The location of this organ transversing the mediastinum and possessing so many vital relationships with structures not otherwise easily shown radiographically, serves to make it an invaluable indicator of disturbances not otherwise readily determined With careful roentgenoscopy, accompanied by appropriate films, it is usually possible to determine whether an esophageal defect is extrinsic or intrinsic. In instances of obstruction caused by tumor, the entire extent and general character of the invasion may be seen, whereas at times these cannot be fully judged endoscopically. Primary lung cancer can present initially with symptoms suggesting an esophageal obstruction When endoscopy and biopsy have failed to establish which site is the primary, that is, esophagus or lung, careful roentgen evaluation has occasionally been able to do so

The presence or absence of an esophageal fistula is usually best determined by roentgen examination. One frequently reads that an iodized oil should be employed for opacification of the esophagus when a fistula is suspected so that any entry of the material into the lung will not be harmful Our experience disputes this because the iodized oils, being prone to droplet formation and failing to cling to mucous surfaces or enter into tiny apertures, are poor substances for outlining the esophagus and depicting fistulas. It is usually far more important to the patient that an accurate diagnosis of his condition be made than that service be paid to the chance that barium may enter and damage the lung, and therefore we regularly employ barium, taking care of course to use just as little as possible If any does enter the lungs, it is evacuated promptly.

Direct invasion of the bones of the chest by a peripheral lung cancer sometimes takes place. The roentgen appearance is usually that of a

water density mass within the lung associated with an irregular area of rib destruction, tending to be contained within the lung mass and to be smaller in extent. The bone involvement is generally lytic, there being no productive or dense element present in the radiograph. Sometimes as many as three or four ribs in the area are affected. One can usually postulate that the whole process is due to a lung cancer rather than to a blood-borne metastasis to either rib, sternum, or vertebra as the case may be, because the margin of the mass in the lung is indistinct and because the water density lung mass is so located in regard to the bone destruction as to indicate that it was bone rather than lung that had been invaded. At times a sheet of tumor may be noted involving the lung, pleura, ribs, and the muscles of the chest wall or diaphragm, in a solid mass.

The pleura may be found thickened and of course pleural fluid is very commonly present. Sometimes the fluid is so extensive that the underlying lung lesion is not visible on routine film studies and special films are needed to demonstrate the tumor. Experience has indicated to us that removal of the fluid in an attempt to show the underlying lesion on subsequent film is not a regularly successful procedure. This may either be because insufficient fluid can be procured or because a pleural thickening due to tumor or to infection remains to hide the lung abnormality. If air is introduced or a pneumothorax develops, a nodularity of the pleura may be easily observed, but this may be caused by tumor or inflammation, so that a completely reliable x-ray diagnosis of pleural metastasis often cannot be made.

The third major category of findings in the roentgen recognition of lung cancer is related to the metastases from the primary cancer. As with the primary tumor, one deals first with the appearance of the individual metastases and then with the effects caused by them. This routine is applied initially to those deposits that occur in the thorax, and then to the metastases taking root outside the chest.

Some of the most characteristic roentgen findings for cancer of the lung are provided by metastases at the lung root. While certain inflammatory diseases may be associated with some degree of lung root enlargement, the circumstance of a density in the lung and an enlargement of the same hilum is most regularly seen with lung cancer. At times the metastatic mass may be so large as to overshadow or even completely hide the primary tumor. There is nothing inherently specific in the way that a lung root cancer metastasis appears roentgenologically. The hilar mass is of water density, the margins may be fairly distinct and somewhat lobulated, and the normal constituents of the lung root are blotted out. It may be that the secondary deposit in the lung root corresponds satisfactorily to the drainage area of the primary tumor, but this is not always so. Sometimes both lung roots may be enlarged by metastases from a

lung cancer. Contrast visualization, bronchography, and tomography may be helpful in revealing the nature of puzzling lung root enlargements.

Another location for metastatic deposits carrying considerable diagnostic weight in the roentgen diagnosis of a lung cancer, is in the mediastinum. Such a deposit is usually on the same side as the primary tumor, but occasionally a crossed deposit is seen, particularly on the right, with none being detectable roentgenographically on the side of the tumor. The secondary mass is homogeneous and of water density with borders tending to be lobulated These metastases in lung root and mediastinum tend to maintain their original homogeneous texture, calcification or liquefaction not being seen as growth continues Careful film analysis coupled with a knowledge of the routes of lymph node drainag and the location of the different mediastinal nodes, will sometimes allov the roentgenologist to name the specific node or groups of nodes that are involved. Too often, however, the nodes are found to be massive and matted, with many groups being affected.

The presence of a water density mass anywhere in the lung field associated with any degree of lung root enlargement should make a roentgen diagnosis of lung cancer the first consideration. If there is also mediastinal adenopathy on the same side then the roentgen diagnosis is more certain. Once in a while one can encounter a lung cancer with no evidence of lung root enlargement but with a mediastinal deposit. Here again the x-ray diagnosis should be fairly reliable When findings due to bronchial obstruction are also identified, the diagnosis would seem quite certain Evidence of other metastases to the pleura, bone, or opposite lung makes the diagnosis of the disease almost unquestionable

The metastases of a primary lung cancer to the lungs are similar to lung metastases from many other cancers They tend to be multiple and o present no particular x-ray characteristic that would lead the roentenologist to guess their primary source. Nodular water density deposits redominate, but at times a patchy infiltrative type of shadow may be und, or rarely one may see both miliary and lymphatic forms. Distant etastases to the bones of the chest are fairly constantly osteolytic, show- little or no increased density formation in the x-ray. These bone castases are so commonly seen in the ribs and other bones of the chest, it behooves the roentgenologist to search every film carefully for At the least suspicion, bone studies with moving grid technique be obtained for confirmation

tastatic deposits to the pleura may be seen as nodular thickenings of is size Naturally they are usually best demonstr
neumothorax and th
l pleural surfaces as ... seen along e ... e presence
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its metastases is quite uncommon Most episodes of pneumothorax due to tumor are found with metastatic sarcomas. The development of pleural fluid may be caused by the pleural metastases

In short, all those conditions due to pressure or actual invasion of different organs such as the bronchi, lung, pleura, vessels, nerves, heart, pericardium, diaphragm, bones, and chest wall, which have been described before in connection with the primary tumor, can be brought about by the metastatic deposits Generally speaking, however, the bronchial effects tend to be much less freqeunt in the case of the metastases

Sometimes those metastases taking root outside the chest may provide the outstanding clinical feature of the disease, causing the patient to appear with the picture of brain tumor, primary bone tumor, spontaneous fracture, or hoarseness. One allied clinical state deserving particular mention though not related to distant metastases outside the chest is that of pulmonary osteo-arthropathy Any case of "rheumatism" having been examined roentgenologically and having a symmetrical periosteal reaction of the parallel type along the tubular bones of the arms and legs must have a roentgen examination of the chest, to determine whether a cancer of the lung is present as the cause of the patient's complaints

The final step in forming an x-ray diagnosis in lung cancer concerns relating the different x-ray findings to the known life history of the disease. Information derived from serial films on many patients with lung cancer indicates that the duration of lung cancer from the time it can first be detected on a chest film to the symptomatic stage can be much longer than previously suspected Several lung cancers in our experience have shown slow growth over a period of several years and others are reporting a similar experience The roentgenologist therefore must be prepared to broaden his concept of the over-all duration of this disease which heretofore has been based upon the length of life after symptoms developed. When one realizes how slowly some of the small lung cancers may grow, another argument against the folly of using uncontrolled interval studies in order to arrive at an x-ray diagnosis is provided

The subject of roentgen diagnosis cannot be completed without giving special emphasis to the detection and diagnosis of the early, usually

tumor discoverable is that of the tiny nodule out in the lung field Unfortunately there is nothing to distinguish this from a number of other lesions having a similar roentgen appearance Therefore, the only safe

way is to take an aggressive attitude towards these innocent looking lesions, after the basic clinical and laboratory work-up has been done, their removal and histologic examination must be carried out The roentgenologist may need to develop techniques to localize these tiny lesions more precisely, both before operation or, if necessary, at the operating table

Another significant x-ray finding for early lung cancer detection is a slight fullness in one lung root Even a minor degree of enlargement must be regarded with considerable suspicion, and appropriate studies, including those of diagnostic roentgenology, should be employed at once. Also any localized aeration change in the lung should be suspected because occasionally an area of emphysema may be the first x-ray clue to the presence of an endobronchial cancer Finally, any infection in the lung that does not resolve within the expected time may indicate the underlying presence of a lung cancer.

The greatest satisfaction that the roentgenologist can have is in being the means of bringing to treatment a small resectable lung cancer having an excellent chance for cure. To this end he must strive to improve his equipment and techniques, to increase his experience, and to become more aggressive in the handling of suspicious cases through closer co-operation with his colleagues in the other branches of medicine He must do his part to make competent x-ray diagnosis available to all and to protect patients from inferior and dangerous x-ray studies Perhaps the regular publication of something analogous to the morbidity and mortality statistics of surgery would seem advisable regarding the roentgenologist's work in the x-ray diagnosis of lung cancer. This would help to determine whether his effort is standard and acceptable, and it would provide a valuable means of stimulating improvement. It should also help to protect the public from inferior grades of roentgen diagnosis, which may be just as deadly as unqualified surgery or medicine

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7

Bronchoscopic Examination

HERBERT C. MAIER

The bronchoscopic examination should be regarded as one facet of the diagnostic work-up of the patient with suspected neoplasm of the lung. The endoscopic findings should be correlated with the information derived from the history, physical examination, roentgenograms, and other laboratory data. It follows therefore that the best assessment of the bronchoscopic findings will be obtained when that procedure is performed by one who is also well versed in the diagnosis and therapy of pulmonary diseases of all types. Since the bronchoscopic findings in some cases give crucial information concerning the location and extent of the neoplastic process, close correlation between the endoscopic interpretation and surgical therapy is desirable.

Bronchoscopic examination of the tracheobronchial tree can be an important adjuvant in the diagnosis of some cancers of the lung. It is essential, however, that this procedure be placed in its proper perspective in the complete diagnostic investigation of a particular patient. The location of the abnormal shadow on the roentgenogram is one of the chief guides to the potential significance of a positive or negative bronchoscopic examination. If the central portion of the abnormal density is close enough to the hilar region to permit endoscopic visualization of the involved bronchus, the bronchoscopic findings may be of great significance in differential diagnosis. If, on the other hand, the lesion in question is more peripherally located, bronchoscopy may have limited value except as a means of collecting secretions for cytologic examination. In the rare patient who is proven to have bronchogenic carcinoma in spite of a negative roentgenogram of the lungs, the diagnosis is usually established because an alert physician appreciated the predominant diagnostic role of bronchoscopy when symptoms suggest a central endobronchial lesion (Plate 2-A).

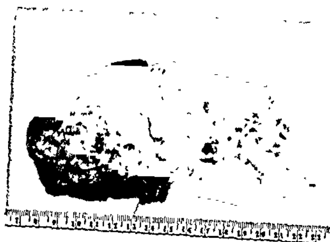
Bronchoscopy may aid in the differentiation of neoplastic and inflammatory lesions of the bronchus. When a tumor is present in the more central portions of the tracheobronchial tree, bronchoscopy may permit direct visualization of the growth and the securing of a biopsy from which

PLATE 2

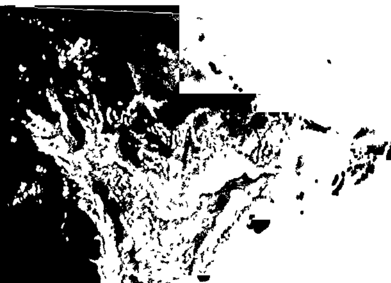
A Right lung removed from a man who had been bronchoscoped because of a transient pneumonitis in the right lower lobe The pulmonary infiltration had cleared on the roentgenogram prior to operation The tiny tumor is seen as a small area of thickening in a branch bronchus of the lower lobe which is located between the 13 and 14 cm mark on the adjacent ruler. Patient alive and well 11 years after operation

B Sagittal section cut through left lung removed from a diabetic patient who had a hemoptysis Tumor is located in the upper portion of the left upper lobe The necessity for telescopic lenses to visualize the fungating growth in the left upper lobe can be seen from the surgical specimen. Patient living and well 11 years after pneumonectomy.









C. Surgical specimen with bronchus cut open demonstrates a granular fu growth characteristic of bronchogenic carcinoma

D Hilar portion of resected right upper lobe shows a smooth rounded tumor with the unattached portion projecting to the line of surgical resection Typical gross appearance of a bronchial adenoma Recognition of the character of the tumor resulted in the sparing of the right middle and lower lobes Similar resection close to a bronchogenic carcinoma would have been an inadequate procedure

a definite pathologic diagnosis can be established (Plate 2-B). Since only a very limited portion of the entire bronchial tree can be visualized through the bronchoscope, even with the aid of telescopic lenses, it should be obvious that the failure to see a tumor in that portion that can be inspected, in no way rules out the presence of a growth in other portions of the lungs.

Considerable confusion has resulted in the minds of many physicians because some endoscopic clinics have reported that a positive bronchoscopic biopsy was obtained in up to 60 or more per cent of their cases of bronchogenic carcinoma. Such data would seem to suggest that a negative bronchoscopy was quite significant in ruling out the presence of cancer of the lung. This is far from the truth because many a patient with bronchogenic carcinoma may show no endoscopic evidence of the neoplasm in the earlier phases of its growth, whereas months later the tumor may be visible through the bronchoscope because of extension medially. Meanwhile, however, the lesion may have metastasized. Therefore if one considers only those bronchogenic cancers which can be seen through the bronchoscope in the earlier phase, the percentage of positive biopsies is quite low. When the radiologically demonstrated pulmonary mass is more peripherally located and does not merge with the normal hilar and mediastinal shadows, few cancers can be biopsied except when the growth is present in the larger bronchial branches of the lower lobes.

Since most cancers of the lung are of bronchogenic origin and tend to ulcerate, cast-off cells from the surface of such neoplasms may at times be obtained by bronchoscopic washings of the segment of the lung with the cancer. The cytologic examination of such secretions and washings may considerably increase the percentage of positive preoperative diagnoses, provided the material is properly collected and then examined by an experienced cytologist. The method of collecting such secretions is described in the chapter on cytology. The utilization of proper technique can do much to improve the value and scope of cytologic diagnosis.

When a bronchogenic carcinoma is visualized bronchoscopically, it often presents as an irregular, nodular, or granular lesion which causes varying degrees of bronchial narrowing (Plate 2-C). The lesion tends to bleed rather readily in many instances. When the presenting part of the lesion is not ulcerated, the extramucosal infiltration of the neoplasm may produce bronchial stenosis with only a smooth or corrugated mucosa visible endoscopically. The presumptive differentiation of the common types of bronchogenic cancer and a benign endobronchial tumor that is bronchoscopically visible is usually not a difficult matter to the experienced endoscopist, although the gross appearance is naturally not to be considered as a final criteria. As the incidence of malignant

tumors of the bronchi increases, the percentage of benign growths becomes less and less. Although twenty years ago benign bronchial tumors were stated to constitute 3 to 5 per cent of the total, such a figure would no longer be correct. Benign endobronchial tumors are especially infrequent in male patients in the cancer age.

Although infection of the bronchi distal to a bronchogenic carcinoma is common, in most instances there is little sign of acute bronchial inflammation proximal to the growth. Caution is necessary in interpreting the significance of a negative bronchoscopic biopsy; it is not unusual to obtain a biopsy which reveals only chronic inflammation because the specimen was obtained at the edge of an ulcerated cancer with secondary infection. To the experienced bronchoscopist the gross appearance of the carcinoma may appear to be so suspicious that the failure of the biopsy to demonstrate cancer may not be given undue significance. Another bronchoscopy may then be indicated in order to obtain a better biopsy.

As previously mentioned, the bronchoscopic findings must be interpreted in conjunction with the history and other data. When diffuse redness of the mucosa of the tracheobronchial tree is noted, an inflammatory process is suggested. Diffuse bronchospasm is more likely to be present in association with inflammation. No single indefinite finding, however, should be given too much weight in itself. One of the lesions which endoscopically, radiologically, and clinically can be readily confused with bronchogenic carcinoma is erosion of a bronchus by a diseased peribronchial lymph node. All preoperative tests may be inconclusive in some such cases because a bronchoscopic biopsy showing only inflammatory tissue does not rule out the presence of neoplasm. In such cases the surgeon must make the final decision on the basis of the operative findings.

Prior to a bronchoscopy the main diagnostic possibilities must be considered so that an appropriate type of endoscopic examination is performed and the proper subsequent laboratory tests of the bronchial secretion are ordered. For instance, if lipoid pneumonia enters into consideration in the differential diagnosis, care must be taken that the instruments do not have any material applied to them that would interfere with the examination for fat droplets in the bronchial secretion. In addition to the cytologic studies of bronchial secretions, appropriate bacteriologic studies are indicated. The significance of the findings must then be analyzed later. The presence of tubercle bacilli or pathogenic fungi does not necessarily mean that a neoplasm may not also be present.

Bronchoscopic examination of the tracheobronchial tree may give indirect evidence of the presence of neoplasm even though such a growth is not directly seen. This is especially true when the disease is advanced

Distortion of the tracheobronchial tree by a firm extrinsic mass, fixation of a portion of the bronchial tree by extrinsic tumor masses with varying degrees of bronchial narrowing, and widening of the tracheal carina are all suggestive evidence of intrathoracic cancer. When the mediastinal lymph nodes are involved by metastatic disease or when there is widespread mediastinal lymphadenopathy, these diseased nodes may interfere with the normal mobility and flexibility of the tracheobronchial tree In the normal individual the tracheobronchial tree elongates and enlarges with each inspiratory effort. There is also an associated shifting of the trachea and bronchi with respiratory and other thoracic motions. In the normal individual the bronchi are so flexible that when a rigid tube like a bronchoscope is inserted, this flexibility is very apparent. In fact, much of the endoscopist's ability to look into smaller branches of the tracheobronchial tree or to inspect areas that are not normally in direct alignment with the trachea depends on this mobility. Therefore when this bronchial mobility is lost because of disease in the adjacent tissues, an experienced endoscopist can detect such abnormalities rather readily Since even severe chronic inflammatory disease with lymphadenitis rarely causes the degree of tracheal or bronchial fixation that is seen with invasive neoplasm, the endoscopic determination of bronchial fixation strongly points to the presence of cancer. When such fixation is present in the smaller bronchi of the lower lobe, it may be due to tumor in the adjacent pulmonary tissue of the lower lobe. In most instances where the fixation is present in the main bronchi or at the orifice of the upper lobes, however, the rigidity of the bronchus is imparted by mediastinal metastases A marked broadening of the angle of bifurcation of the trachea associated with fixation in this region is usually due to tumor masses in the subcarinal lymph nodes which push the two bronchi laterally. Thus bronchoscopic examination can yield considerable information concerning the probable extension of cancer of the lung into the mediastinal lymph nodes and can thus aid in determining the feasibility of surgical therapy.

Bronchoscopic examination is invaluable in giving accurate information concerning the endobronchial extension of a tumor in the hilar portions of the lung or trachea. Whereas preoperative bronchoscopic examina*tion may not always be necessary* when there is an asymptomatic tumor obviously remote from the hilar portion of the lung, bronchoscopy should not be omitted when dealing with lesions anywhere near the range of endoscopic vision. The upper limits of the growth within the tracheobronchial tree should be carefully noted, tracheal and carinal extension may demonstrate that the lesion is not satisfactory for routine pneumonectomy. In any case of cancer of the lung located close to the hilum as seen on the roentgenogram, but where for one reason or another

lobectomy may be considered as preferable to pneumonectomy, a preoperative bronchoscopy may help in deciding whether a limited resection is at all feasible. Whenever a cancer can be directly seen through the bronchoscope, it is rarely feasible or desirable to do a less radical resection than pneumonectomy unless the surgeon is dealing with one of the rarer, less malignant tumors, such as the bronchial adenoma (Plate 2-D).

When a bronchogenic carcinoma extends close to the trachea, knowledge concerning the upper limits of the growth are of utmost importance to the surgeon. The proximal extension of the neoplastic infiltration may be such as to preclude complete extirpation without associated tracheal resection. Although the thoracotomy often reveals the extrabronchial extension to be more extensive than the invasion of the bronchial wall itself, it is essential that the intraluminal and intramural involvement be assessed endoscopically before operation. Submucosal infiltration usually extends a varying distance beyond the site of gross neoplastic lesion. Biopsy of the submucosa proximal to the growth at the site of anticipated surgical transection of the bronchus may reveal whether neoplastic tissue would be cut across. Some endoscopists recommend that a biopsy of the carina be obtained at bronchoscopy in all cases where the apparent involvement extends close to this region. If such a carinal biopsy were found to have cancer cells, the lesion would usually be considered to be too advanced for surgical eradication.

Bronchoscopic examination should always include an inspection of the larynx. Any impaired motion or paralysis of the vocal cord should be carefully noted. The upper trachea should also be carefully inspected. Although tracheal neoplasms are rare, we have seen several such cases in which the diagnosis was missed on the first bronchoscopic examination because the operator overrode the tumor on the initial insertion of the bronchoscope and apparently did not carefully examine the trachea as he withdrew the instrument. When a patient manifests stridor or has a brassy type of cough, tracheal narrowing is likely to be present. A bilateral wheeze requires consideration of tracheal pathology. The presence of dyspnea and harassing cough that cannot be explained on the basis of pulmonary radiologic findings, also requires the ruling out of tracheal abnormality by thorough endoscopic visualization. Not infrequently the tracheal compression is caused by metastatic disease in the paratracheal lymph nodes; this is far more common than intraluminal extension of the bronchogenic carcinoma.

There is one group of patients with cancer of the lung in whom the advisability of bronchoscopy should be carefully weighed before deciding whether this examination is wise. When there is swelling of the head and neck as a result of vena caval obstruction, bronchoscopy may entail special hazards. In such cases the obstruction to venous and lym-

phatic drainage from the head and neck may result in considerable edema of the larynx If dyspnea is already a problem, the slightest added mucosal trauma by endoscopy can create a serious or even critical situation Most lung cancers which produce the vena caval syndrome are located along the paramediastinal portion of the right upper lobe above the orifice of the upper lobe bronchus. Thus they are usually not accessible for direct bronchoscopic biopsy. It seems ill-advised, therefore, to perform a bronchoscopy in this group at a time when it is hazardous and unlikely to give worthwhile information If bronchoscopic examination is considered indicated, it can be performed a few weeks later, after the swelling of the head and neck has receded following radiation therapy or chemotherapy

Bronchoscopic examination for neoplasm in adults can be done most safely with topical anesthesia after adequate sedation Properly applied topical anesthesia together with gentleness in the introduction and manipulation of the bronchoscope are the chief requirements for successful examination If these requirements are met, the author does not feel that general anesthesia is necessary Some endoscopists and patients, however, prefer intravenous anesthesia together with a muscle relaxant. Alarming bronchospasm may occasionally occur when bronchoscopy is done under general anesthesia, especially with certain drugs. Reactions to cocaine or other topical anesthetic agents can be reduced to a minimum by avoiding excessive quantities of anesthetic agents. One should desist from spraying a large quantity of cocaine onto a mucous membrane which has already been abraded by an unsuccessful attempt at endoscopic examination Such maneuvers greatly increase the possibility of a drug reaction

In some quarters, both among physicians and patients, bronchoscopic examination is regarded as a very disagreeable and distressing experience This attitude is unjustified when the procedure is performed by a skilled and gentle endoscopist. Although there is considerable individual variation on the part of patients, partly influenced by their gagging tendency, anatomical contour of neck and throat, and emotional stability, bronchoscopy should be associated only with minor discomfort. Proper sedation before the procedure is most important Minimizing the disturbance entailed by bronchoscopy will make the procedure more readily acceptable to physician and patient whenever this examination is indicated, as at the first slight su [illegible] the

Repeated bronchosc [illegible] nnot piecemeal removal of [illegible] be surgically resected or satisfactorily treated by roentgen rays. This applies chiefly to certain benign endobronchial tumors and rarely to malignant neoplasms. If the tumor is vascular, great care must be taken to avoid obstruction of the airway and asphyxia due to aspiration of the

blood into the bronchi. When a lesion in the trachea is being treated by this means, the danger is particularly great when one lung is already functionless and blood tends to run into the bronchus of the normal lung. A double suction system should be available in such instances in case one gets blocked with clotted blood. A bronchoscope with an attachment for electrocoagulation should be employed in such rare instances The special situations in which peroral endoscopic treatment of bronchial tumors is indicated is considered further in the discussion of these specific tumors

The advisability of performing a bronchoscopy while the patient is expectorating blood depends on the amount and persistence of the hemoptysis as well as the type of information being sought If only slight blood streaking is present, the bronchoscopy need not be postponed When larger quantities of blood are being expectorated, the question of delaying the endoscopic examination depends on whether the site and source of the bleeding are known A routine bronchoscopy for biopsy of a radiologically demonstrated tumor had usually best be delayed until the bleeding has subsided, the visualization of the growth is then more satisfactory. When the nature of the lesion and its site are not definitely known it may be advantageous to perform the bronchoscopy during the time of hemoptysis in selected cases, so that the bronchus from which the blood is coming may be located.

In addition to its place in the preoperative recognition of bronchogenic carcinoma, bronchoscopy may be required in the management of complications after surgery and the investigation of postoperative suspected recurrences of neoplasm When a patient has some blood-tinged expectoration a few months or later after a pulmonary resection for lung cancer, a bronchoscopic examination is indicated to determine whether there is evidence of recurrent neoplasm at the bronchial stump Sometimes the presence of granulation tissue without neoplasm may be the cause for such bloody expectoration

Bronchoscopy plays a very important role in those cases in which there is postoperative retention of bronchial secretions that cannot be satisfactorily evacuated by coughing and tracheal suction. Such therapeutic bronchoscopies should be done with minimal sedation and topical anesthesia so that the cough reflex is not impaired.

8

Exfoliative Cytology in Diagnosis of Lung Cancer

GEORGE N. PAPANICOLAOU
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INTRODUCTION

HISTORICAL NOTES

Fragments of tumor were described in sputum more than one hundred years ago (1), and attempts to identify tumor cells in unstained material were reported as early as 1887 by Hampeln (2). Wet films were studied by Dudgeon and Patrick (3) and were reported to have been used successfully in the diagnosis of cancer by Dudgeon and Wrigley (4). When the cytologic method became widely applied in the study and diagnosis of uterine tumors, after the monograph of Papanicolaou and Traut in 1943 (5), its logical extension to sputum and bronchial secretions followed shortly Wandall's cytologic and statistical study (6), published in 1944, is an early landmark. In 1946 Papanicolaou (7) pointed to the advantages offered by the application of cytologic techniques, as developed in the study of the vaginal secretion, to the diagnosis of cancer of the respiratory and other systems. In the same year Herbut and Clerf (8a, 8b) emphasized the value of bronchoscopically obtained secretions. Soon reports of a large-scale application of the method were forthcoming (Woolner and McDonald) (9). The statistical requirements for evaluation of the procedure were critically considered by workers at Yale (Liebow *et al* (10), Harris (11)) The monograph by Farber and associates (12), and the Papanicolaou atlas (13) not only reviewed previous work but presented the results of extensive experience, and described and illustrated criteria for the diagnosis of different types of lung tumors. Progress is constantly being made in the application of cytologic methods to the study and diagnosis of pulmonary disease including neoplasms This work, however, must be regarded as still far from complete

ESSENTIALS OF A CYTOLOGIC LABORATORY

The essentials of a laboratory for the cytologic study of cancer of the lung are 1) a skilled and experienced cytopathologist upon whom falls the responsibility for the final diagnosis, 2) technicians well trained in cytologic procedures, who are capable of preparing and "screening" the smears, and 3) adequate equipment and facilities. Such a laboratory should evaluate itself periodically against the measure of a well-established final diagnosis. For this purpose a series of "unknowns" should be employed containing at least 40 per cent of slides from patients without carcinoma, but with such diseases as bronchiectasis, tuberculosis, and lipoid pneumonia that may be the source of confusing cells. This procedure will justify confidence in a good cytologist or laboratory, and will bring to light any deficiencies in a poor one.

TECHNIQUE

Material for a cytologic study can be obtained from the lung with relative ease. A simple and rich source of supply is always available in the mucous secretion which fills the bronchi and contains many exfoliated or migratory cellular elements. A deep cough specimen of sputum collected preferably in the morning usually provides adequate material for a cytologic examination. A specimen of saliva is, of course, unsatisfactory and can be recognized microscopically by the absence of dust cells and the predominance of superficial squamous cells.

Sputum specimens should be brought to the laboratory as soon as they are obtained from the patient. Ideally this should be done by a technician who can directly instruct the patient in cleaning the teeth and mouth and in methods of producing true sputum. The time and effort necessary to perform this task will be well repaid in the suitability of the slides prepared for examination.

To prevent the deterioration of the cells resulting from the growth of microorganisms, sputum specimens which cannot be processed promptly may be collected into a bottle containing 70 per cent alcohol. A label giving the name of the patient and the date should accompany the bottle.

A number of smears—usually three to five—are prepared from each sample, preferably from selected bloody or otherwise suspicious areas of the sputum. With alcoholized specimens, the secretion tends to adhere better to slides which have been previously coated with a thin layer of Mayer's albumen, but this is not necessary with sputum freshly obtained. The smears are fixed for an hour or longer in a solution of equal parts of 95 per cent alcohol and ether. Since there is no specific method

for staining cancer cells, various methods can be used for staining cytologic smears. A procedure found to give satisfactory results in sputum smears is as follows:

STAINING PROCEDURE 267 (13)

1. Transfer slides, without drying, from the ether-alcohol fixative to 80 per cent alcohol and run through 70 per cent and 50 per cent alcohols into distilled water, leaving in each solution approximately ½ min.
2. Stain for 4 min. in Harris' hematoxylin made without acetic acid and diluted with an equal volume of distilled water.
3. Rinse in distilled water.
4. Dip in 0.25 per cent hydrochloric acid five to six times.
5. Place in running tap water for 6 min.
6. Rinse in distilled water and transfer through 50, 70, 80, and 95 per cent alcohols, leaving in each solution approximately ½ min.
7. Stain in OG-6 (14) for 2 min.
8. Rinse in 95 per cent alcohol, three changes.
9. Stain in EA-65 (15) for 2 min.
10. Rinse in 95 per cent alcohol, three changes.
11. Dehydrate and clear by running through: 1) absolute alcohol, 2) absolute alcohol and xylol, equal parts, and 3) xylol, leaving in each solution long enough for the smears to be thoroughly penetrated and thus dehydrated (approximately ½ min).
12. Mount, without drying, using a coverslip and permount, gum damar, Canada Balsam, or any other neutral mounting medium. (Acid or basic mounting media will alter the staining reactions and often cause fading of the stains.)

A bronchoscopic examination of the patient affords the opportunity of obtaining a purer specimen of bronchial secretion by aspiration or lavage with a small amount of physiological saline solution.

Several methods of collecting secretions with the use of the bronchoscope have been practiced. The simplest procedure involves the use of a cotton or gauze pledget held in a bronchoscopic forceps. This provides direct access to material situated on the surface of a particular bronchus. If the tumor is within reach of the forceps, this method is ideal, but a biopsy can then be obtained just as easily. In many instances, however, the tumor is not directly accessible and various aspiration methods are preferable, since they may provide material from distally located tumors. Aspiration may yield abundant secretions, but if these are absent or scanty, isotonic saline solution can be introduced to wash the peripheral bronchial surfaces. The method recommended by McKay *et al.* (16), who have

had an extensive experience, is to introduce a small portion of cotton into a special aspirating cannula. This acts as a filter for fragments of mucus and tissue which may then be smeared on a slide. Perhaps the commonest method is the collection of secretions or washings into a trap connected to a suction cannula. This method yields the best results if no saline is used, and if the material is quickly smeared. The saline solution is far from "physiological." Cells allowed to remain within this solution tend to round up, to shrink, and to stain poorly.

Smears prepared from the sediment obtained after centrifugation of a bronchial aspiration or washing specimen are handled in the same way as smears prepared from sputum. Excess sediment may be fixed, embedded in paraffin, and sectioned for a microscopic examination. A pathologic evaluation of the sections of a cell block made from sediment of a bronchial aspirate or from sputum may add to the accuracy of the diagnosis (17).

A short fixation and pre-embedding technique for sediment specimens may be outlined here for the benefit of those who would like to experiment with it.

1. Fix in a solution of 95 per cent alcohol and ether for 1 to 2 hrs.
2. 95 per cent alcohol ½ hr.
3. Absolute alcohol (two changes) 1 hr.
4. Absolute alcohol and xylol ½ hr.
5. Xylol 1 hr.
6. Xylol and paraffin (on top of oven) ½ hr.
7. Paraffin, embed.

With this short technique, sections may be cut, stained, and examined within a day.

NORMAL AND NON-NEOPLASTIC EXFOLIATIVE CYTOLOGY OF SPUTUM AND BRONCHIAL SECRETION

A thorough knowledge of the normal cell types encountered in bronchial secretions and of the range of their variability is very essential for an efficient cytologic evaluation of smears. Structural anomalies of cells as seen quite frequently in chronic inflammatory and other non-malignant pathologic conditions of the respiratory tract should also be properly understood. Adequate evaluation of a cytologic preparation is based on the consideration of positive criteria of malignancy, which connotes the ability to recognize and rule out atypical cytologic features simulating malignant changes.

The exfoliative cytology of the bronchial secretion differs from that

of the sputum in that it is free from contamination by cells of the squamous type derived from the upper part of the respiratory tract, *i e*, oral, pharyngeal, and laryngeal regions. It is therefore more pure, as it consists chiefly of cells lining the bronchial mucosa, with only occasional pharyngeal cells carried in with the bronchoscope Most of the bronchial epithelial cells are well-differentiated columnar or cuboidal cells and belong to either the ciliated or the goblet type.

The ciliated cells (Plate 3-1) can be identified by the cilia, or in their absence (which is not infrequent in the exfoliated state), by the dense cuticular cell border The nucleus is usually oval and situated centrally or near the proximal end of the cell. It is well supplied with chromatin that shows a granular distribution. Bi- or multinucleation (Plate 3-2) is not infrequent Para- or perinuclear vacuolation of the cytoplasm is commonly seen.

The goblet cells (Plate 3-3) can be identified by their characteristic shape and by their basally located nucleus, which may be pressed into a cuplike form. The cytoplasm is filled with a mucoid secretion, giving it a vacuolated appearance

The smaller undifferentiated "reserve" cells that compose the deeper layers of the bronchial epithelium can be identified more confidently when in clusters (Plate 3-4).

The two differentiated types of normal bronchial epithelial cells, the ciliated and goblet, and the undifferentiated reserve cells, are usually seen in bronchial secretion smears In sputum their presence is much less frequent. On the other hand, the sputum contains, as a rule, many squamous cells exfoliated from the upper portion of the respiratory passages These may be separated into two main groups the superficial squamous (Plate 3-5), and the deeper or parabasal cells (Plate 3-6). Squamous cells, many of which are derived from the oral mucosa, are usually found in large numbers in specimens produced by expectoration rather than by deep coughing.

Histiocytes and polymorphonuclear leucocytes--particularly neutrophils--are a frequent constituent of both sputum and bronchial secretion smears The histiocytes may be divided into two groups those containing dust or carbon particles, the so-called "dust cells" (Plate 3-7) which are characteristic for the respiratory tract and are found in both normal and pathologic conditions, and those devoid of dust or carbon granules which are often prominent in acute or chronic inflammatory processes In such inflammatory reactions the histiocytes exhibit higher phagocytic activity and greater variability in size and form, with the occasional appearance of large multinucleated forms (Plate 3-8). The histiocytes can be recognized by their foamy cytoplasm, their poorly defined cell

borders and loose grouping, the presence of inclusions indicating a phagocytic action, and their frequently kidney-shaped nuclei.

In tuberculous and some other chronic infections the histiocytes may assume an epithelioid form which makes them almost indistinguishable from epithelial cells. In lipoid pneumonias the histiocytes (lipophages) are loaded with lipid droplets. When these are dissolved the cytoplasm is left with large vacuoles by which these cells may be easily identified (Plate 3-9). In cases of silicosis the histiocytes are loaded with silicate particles. Lymphocytes usually appear in small numbers and have a limited diagnostic significance. Their presence in large aggregations is rather rare (Plate 3-10).

In inflammatory and other pathologic conditions, exfoliated cells often exhibit atypical features, which may be sufficiently characteristic to permit the recognition of some distinctive cell types. One of these is the so-called "Pap" cell,* which is frequently encountered in sputum and bronchial secretion smears, chiefly in chronic or acute inflammations of the lung. Cells of this type are relatively small and have an elliptic form and an elongated and usually pyknotic nucleus (Plate 3-11). The nucleus may show fading, which is an indication of necrosis (Plate 3-12). It is likely that "Pap" cells represent a metaplastic change of undifferentiated reserve cells of the bronchial mucosa. Their diagnostic significance is still obscure. Their occasional presence in cases of proven epidermoid carcinoma of the lung may suggest that they represent a precancerous change. However, this is not necessarily true since in such cases their presence may be due to a concomitant chronic inflammatory process. In the case mentioned above, which has been followed for a period of eight years, no malignant deterioration has been observed.

Larger cells showing squamous metaplasia (Plate 3-13) may also be seen occasionally in sputum and bronchial secretion. Their identification is safer in bronchial secretion because sputum often contains many squamous parabasal cells with which the larger metaplastic cells may be easily confused (compare Plate 3-13 with Plate 3-6). Such large metaplastic cells are sometimes seen in smears containing "Pap" cells. They have also been noted in some cases of proven epidermoid carcinoma. Their staining reaction is usually acidophilic as is that of both the "Pap" cells and the malignant epidermoid cells. As a rule they do not exhibit abnormal cytoplasmic or nuclear features that would warrant their interpretation as malignant. However, the possibility of a precancerous or early cancerous nature cannot be ruled out.

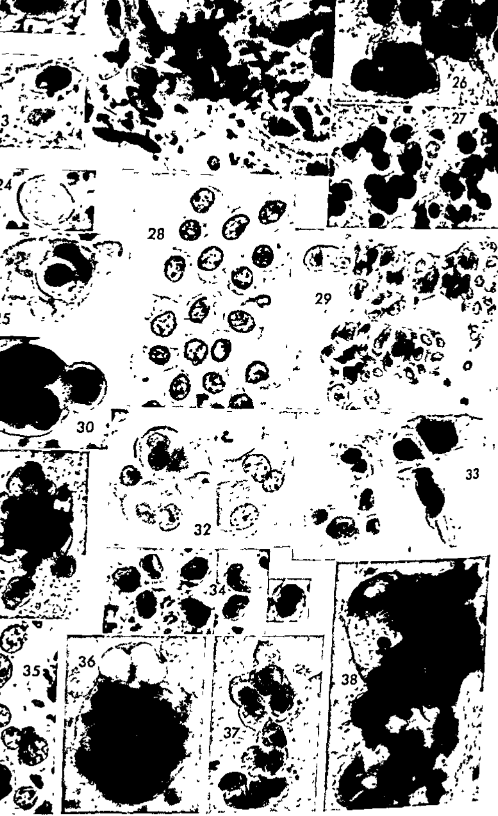
* This name was assigned to this cell type at the Papanicolaou Cytology Laboratory where it was first observed in 1947 in a sputum specimen of the senior author during a period of an acute upper respiratory infection.

The illustrations in Plates 3 and 4 are photomicrographs of cells and cell clusters from smears stained with the Papanicolaou OG EA stain. Magnification X600 (Photomicrograms and plates prepared by Constantin Railey.)

PLATE 3

1 Normal ciliated cells Bronchial washing
2 Multinucleated ciliated cells, nonmalignant Sputum.
3. Normal goblet cells Bronchial washing
4 Normal bronchial epithelial reserve cells Bronchial washing
5 Normal superficial squamous cells Sputum.
6 Normal parabasal squamous cells Sputum
7 Histiocytes of the lung (dust cells) Sputum.
8 Multinucleated dust cells Sputum
9 Highly vacuolated histiocytes (lipophages). Sputum Chronic lipoid pneumonia
10 Aggregation of lymphocytes Sputum No evidence of disease
11 Cluster of "Pap" cells Sputum Primary atypical pneumonia
12 "Pap" cells with nuclear fading Sputum Congestive pulmonary disease with hemoptysis
13 Cells showing squamous metaplasia Sputum Nonspecific pneumonitis
14 Cluster of atypical cells Sputum. Bilateral bronchiectasis
15 Cluster of atypical cells with indication of squamous metaplasia. Sputum Sa case as 14 above
16 Ciliated cells, one with a large atypical nucleus Bronchial washing Foreig body with reactive pneumonitis and pleural effusion
17 Ciliated cell with a large and hyperchromatic nucleus Bronchial washing Bronchogenic carcinoma with metastasis to liver and spleen
8 Epithelial pearl Sputum Possible acute bronchitis with hemoptysis of unknown etiology
Epithelial pearl Sputum Epidermoid carcinoma of the lung with generalized metastasis
Curschmann's spiral Sputum Chronic pulmonary disease with hemoptysis


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PLATE 4

21 Malignant cell Sputum Bronchogenic carcinoma
22 Malignant cells, epidermoid type Sputum Squamous cell carcinoma of the lung
23 Two malignant cells, one with faded nucleus Sputum Same case as 21 above
24 "Ghost" cell Bronchial washing Epidermoid carcinoma of the lung
25 One malignant cell engulfed by another Sputum Same case as 21 above
26 Malignant cells, undifferentiated type Bronchial washing Bronchogenic carcinoma
27 Malignant cells, anaplastic type Sputum Oat cell carcinoma of the lung
28 Malignant cells Sputum Adenocarcinoma of the lung
29 Clusters of malignant cells Sputum Terminal bronchiolar carcinoma A section of the tumor from the same case is illustrated in following chapter
30 Multinucleated malignant cells Sputum Terminal bronchiolar carcinoma Primary diagnosis by the smear examination.
31 Cluster of neoplastic cells Bronchial washing Adenoma of the bronchus
32 Malignant cells Sputum Carcinoma metastatic to the lung from the breast
33 Malignant cells Sputum Rhabdomyosarcoma metastatic to the lung from the thigh
34 Malignant cells Sputum Reticulum cell sarcoma metastatic to the lung
35 Malignant cells Sputum Melanoma metastatic to the lung from the thigh
36 Cluster of malignant cells Sputum Adenocarcinoma metastatic to the lung from the pancreas
37 Malignant cells Bronchial washing Carcinoma metastatic to the lung from the tongue
38 Cluster of malignant cells Sputum Adenocarcinoma metastatic to the lung from the lower sigmoid

Atypical clusters of exfoliated cells with a pattern simulating that of neoplastic cells may sometimes be seen in cases of bronchiectasis (Plate 3-14). The cells appear to be of [illegible]
The configuration of the cluster [illegible]
papillary projections of the bro[illegible]
logic specimens in this disease. The benign nature of the cells is revealed by the regularity of their grouping pattern and the uniform size and structure of their nuclei. Cell enlargement and metaplasia may also be observed (Plate 3-15). In cases with a coexisting infection the cells are sometimes infiltrated by leucocytes.

No plausible explanation has as yet been offered for the relatively frequent occurrence of multinucleation (Plate 3-2) and of various nuclear abnormalities (Plate 3-16, -17) in exfoliated ciliated cells. These atypical [illegible]

they are not as clearly indicated in tissue sections as in smears in which the cells are preserved in toto. The question of whether the presence of cilia in cells with distinctly abnormal features is by itself a proof that such cells are not malignant, cannot be satisfactorily answered at present.

Typical epithelial pearls are rather rare in bronchial smears but may be seen occasionally in malignant as well as in nonmalignant cases (Plate 3-18, -19). Their nature is revealed by the structure of their cellular components Pearls found in sputum may sometimes be derived from the esophagus, where they develop more frequently. Pearl-like structures consisting of two cells, one enveloping the other, are more commonly seen in smears from the respiratory tract in cases of carcinoma of the lung, and may sometimes give a clue as to the presence of malignancy

Curschmann's spirals (Plate 3-20) can be easily recognized in sputum smears due to their characteristic structure and their deep staining with hematoxylin They may be seen in smears from asthmatic patients, but also in other chronic inflammatory conditions.

CRITERIA OF MALIGNANCY

Cells exfoliating from malignant neoplasms of the respiratory tract are found in sputum and bronchial secretion smears singly, in clusters, or occasionally in small tissue fragments The criteria by which their malignant nature is recognized are thus based partly on the structural characteristics of the individual cells and partly on their interrelationships Though a positive diagnosis of a malignant neoplasm may sometimes be made on the strength of single abnormal cells, the most conclusive evidence is usually afforded by the presence of cell clusters or small tissue

fragments which give an insight into the architectural pattern of the tumor

Some of the cytologic criteria of malignancy are common to all kinds of malignant cells of various organs, whereas others are more specific as they apply only to some distinctive cell types Of the general criteria, the most important are those pertaining to changes in the nucleus, such as disproportionate enlargement, high chromatin content, aberrant chromatin patterns, prominence of nucleoli or karyosomes, multinucleation, abnormal mitosis, marked thickening of the nuclear membrane, atypical contour, pyknosis, and various degenerative changes

Criteria based on cytoplasmic changes, though generally less conclusive, are also contributory to the diagnosis Of these the most significant is perhaps the pronounced acidophilia or orangeophilia of cells exfoliating from bronchogenic epidermoid carcinoma In other types of neoplasms of the lung, such as the bronchogenic undifferentiated carcinomas, the exfoliated malignant cells tend to be distinctly basophilic

Vacuolation of the cytoplasm is more frequently observed in adenocarcinomas or terminal bronchiolar carcinomas In some cases of metastatic melanoma, melanin granules may be seen in the cytoplasm of malignant cells and as phagocytosed particles in histiocytes Cytoplasmic inclusions of leucocytes and of cellular debris in malignant cells are more frequently observed in adenocarcinomas.

The most striking modifications in the form and type of the exfoliated cells are encountered in bronchogenic epidermoid carcinomas, in which some malignant cells may grow to giant sizes and assume very aberrant forms Degenerative and necrotic changes are seen rather commonly in smears from all types of malignant neoplasms and constitute one of the most valid criteria of malignancy Deformation, gradual fading, or complete resorption of the nucleus results in characteristic degenerative patterns in cells of the bronchogenic epidermoid carcinomas Different patterns of necrosis may be observed in other types of neoplasms such as adenocarcinomas, oat cell carcinomas, or malignant lymphomas The necrotic cells of the lymphoid type often show a karyolytic pattern which contrasts to the nuclear pyknosis usually exhibited by degenerating malignant cells of the oat cell type Cytolysis is also commonly seen in carcinomas of this latter type

Clusters of malignant cells or small fragments of malignant tissue, when present, add greatly to the diagnostic value of the smears They usually exhibit irregular patterns which contrast to the orderly arrangement of the cells in nonmalignant clusters Dense grouping and crowding of the cells and their nuclei, lack of distinct cell boundaries, anisocytosis, anisokaryosis, and engulfment of one cell by another are additional diagnostic points. The grouping of the malignant cells may sometimes give rise

to distinctive patterns as in adenocarcinomas, oat cell carcinomas, or malignant lymphomas.

Blood cells and histiocytes are almost always present in sputum and bronchial secretion smears but are more conspicuous in acute and chronic inflammatory conditions. In cancer of the lung their number varies considerably and their diagnostic significance is thus limited. Fresh blood is not as suggestive of cancer as is old blood. In bronchial secretion specimens obtained by bronchoscopy, the presence of blood is often due to trauma and, therefore, loses some of its diagnostic value. Histiocytes with atypical features may appear in cancer as well as in inflammatory and other conditions. Conspicuous aggregations of lymphocytes, though not diagnostic, may sometimes suggest the presence of a malignant lesion

The ultimate goal of the cytologist and cytopathologist is to learn how to recognize and identify each of the more specific and representative types of normal, nonmalignant, and malignant cells appearing in sputum and bronchial secretions This can be achieved only by long study and experience

EXFOLIATIVE CYTOLOGY OF NEOPLASMS OF THE LUNG

The exfoliative cytology of tumors of the lung presents a variety of patterns depending primarily upon the cytologic type of the tumor. For the purpose of a close correlation the description of these cytologic patterns will follow the order of the classification system adopted in the chapter on pathologic aspects.

I. Primary malignant epithelial tumors

A. Bronchogenic

1. Epidermoid carcinoma

The exfoliative cytology of the epidermoid carcinoma of the lung may be subdivided into two types

a Squamous cell type

This is the most frequent type of carcinoma and is characterized by a very distinctive cytologic pattern In tumors of this kind there is, as a rule, a rich exfoliation of malignant cells of the squamous variety exhibiting wide variations in size and form The cells may be round or oval (Plate 4-21), or may appear in elongated and other bizarre shapes (Plate 4-22). Many cells exhibit intense acidophilia or orangeophilia, a feature which greatly facilitates their detection and identification Their nuclei may show enlargement and true hyperchromasia or display marked degeneration and various stages of resorption (Plate 4-23) which often results in their

complete disappearance, as in the so-called "ghost" cells (Plate 4-24). Engulfment of one cell by another may be seen occasionally (Plate 4-25). Malignant epidermoid cells most frequently appear in smears singly or in small groups, though formation of larger clusters is not uncommon.

b [illegible]

is revealed by their irregular pattern and the abnormal features of the nuclei (Plate 4-26). Because of the relatively large size of the cells, tumors of this type are also known as "large cell anaplastic" carcinomas.

2. Anaplastic carcinoma

Under this heading one might include all types of carcinoma consisting of small undifferentiated cells in contrast to the above-described large-cell undifferentiated epidermoid type. Cytologically, the most characteristic of the small-cell anaplastic carcinomas is the "oat cell" variety. Exfoliated cells from neoplasms of this type, contrary to what might be expected, do not exhibit the typical oat cell form (Plate 4-27). They are mostly round and may sometimes show great resemblance to the reserve cells of the bronchial mucosa. A differentiation between these two cell types is often difficult, particularly in bronchial secretion smears in which epithelial reserve cells are seen quite frequently. Groups of lymphocytes or small monocytes may also be a cause of a false interpretation. Cells exfoliated from oat cell carcinomas often show cytolysis, while their nuclei exhibit pronounced hyperchromasia and irregularity in size and form. Their grouping pattern is rather characteristic of this tumor type.

3. Adenocarcinoma

Cells derived from tumors of this type may be identified by their mucoid cytoplasmic content, which gives them a vacuolated appearance, and by the frequently eccentric position of their nucleus (Plate 4-28). Their glandular nature can be recognized more readily in those cells which have retained their cuboidal or columnar form after exfoliation. Clusters of adenocarcinoma cells often appear in well-organized insular units, with smoothly rounded outlines. They may also occur in long, apparently solid columns. The best-differentiated forms of adenocarcinoma may be indistinguishable from terminal bronchiolar carcinoma or certain metastatic tumors.

these two systems of classification, we may simply point to the fact that the difference between them is actually very slight, since in Papanicolaou's system, Classes I and II are considered as negative, III as suspicious, and IV and V as positive. The subdivision of the negative group into two classes—I and II—permits a distinction between strictly normal and atypical cytologic findings as observed in cases of benign tumors or severe inflammatory reactions. In the positive group the subdivision into groups IV and V serves the purpose of placing more emphasis on findings interpreted as conclusively positive (Class V). It has been shown that with a strict application of cytologic criteria an accuracy approximating 100 per cent can be maintained in Class V reports (18).

CONTRIBUTION OF THE CYTOLOGIC METHOD TO THE DIAGNOSIS OF CANCER OF THE LUNG

The cytologic method is now widely accepted as an important adjunct in the diagnosis of pulmonary neoplasms Any evaluation of the method will seek to establish the increment in the proportion of patients that come to operation with an accurate microscopic diagnosis. This implies a determination both of sensitivity (percentage of correct positive diagnoses) and of error (percentage of false positive diagnoses). There is universal agreement that accuracy in the diagnosis improves with the experience of the observer. This assumes adequate technique in obtaining the sputum and preparing the slides, in staining, and in the thorough "screening" of all available material. It has been demonstrated in several extensive studies that the yield of positive diagnoses increases with the number of specimens examined, with the number of microscopic slides prepared from each specimen, and with the number of competent observers who review the slides.

Actually very few statistically impeccable evaluations have been accomplished. Necessary for this purpose are: 1) A large series of patients in whom the final diagnosis is established beyond peradventure. In the case of dubious lesions, or actual cancer, this would require histologic examination of tissue. 2) The material for cytologic diagnosis to include at least 50 per cent of sputa from patients with confusing, but not neoplastic disease 3) The cytologic diagnosis to be rendered with no knowledge whatsoever of the clinical data, not even the age or sex of the patient. This is necessary if the purpose is to evaluate the work of the cytologist as such, rather than of all of the diagnostic procedures that might contribute to the preoperative diagnosis

Reports of sensitivity between 80 and 90 per cent and of a false positive rate below 2.5 per cent have been published, but the problem, aside from

the question of proper statistical evaluation, is not so much how well the cytologic method can be practiced by the most devoted and experienced cytologists engaged in a special study, but rather how *it is likely to be generally practiced.* When the above-outlined criteria for an unbiased evaluation have been utilized as the basis for an evaluation, the sensitivity of the method has been as low as 50 to 60 per cent, whereas the false positive rate has usually not exceeded 5 per cent. It must be emphasized that these results are subject to great improvement with increasing training. Thus in one experience where the criteria for Class V were strictly applied, the cytologic diagnosis was confirmed in every instance, including some where lobectomy or pneumonectomy was performed on the basis of the cytologic findings alone (18).

In the experience of most observers an increment of 30 to 40 per cent of patients with a positive microscopic diagnosis results when cytologic examination is added to bronchoscopic biopsy (19). This at least doubles, in most hands, the magnitude of this all-important datum. Furthermore a negative result of an attempted bronchoscopic biopsy implies that the lesion is beyond the reach of the bronchoscope, thus the cytologic method makes the more peripheral tumors available for microscopic study. In many cases even the cell type may be determined by an experienced cytologist (20). The cytologic method has been invaluable in the recognition of cancer of the lung where this has been masked by such diseases as concurrent tuberculosis.

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9

The Search for the Early Case

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The increase in the incidence of lung cancer is well-documented and has been discussed in detail elsewhere (1). The search for the early case must be carried on by applying all modalities for detection at all levels. Such a program embraces education of the public, emphasis on the clinical clues of lung cancer to the private physician, and adoption of survey techniques, which will at least encompass the male cigarette smokers of 40 or more years of age.

PUBLIC EDUCATION

This comprises a continuation of programs that inform the laity of the importance of the problem of lung cancer in general, the need for careful re-examination of the male population 40 years of age and older at periodic intervals, and the necessity for medical advice should any of the early symptoms of lung cancer develop. Such a campaign can only be waged successfully by frequent review of the problem, using all the present methods of mass communication.

PROFESSIONAL EDUCATION

This implies the development by all doctors of that [illegible] that has been carefully defined elsewhere as a "high index of suspicion." Again all the methods of dissemination of information should be employed including pamphlets, articles in medical journals, review of the problem in open meetings of county medical societies by lecture and case presentation, and finally, encouragement of consultation between the physician, specialist, and public health officer.

SCREENING OR MASS SURVEY

To date, the chest x-ray is the only practical method of screening patients for lung cancer at the community, hospital, or private physician level. The question of the reliability of the chest x-ray as a method of detection has been debated by some and its limitations and pitfalls emphasized (2, 3, 4). However, a properly taken and interpreted teleoroentgenogram can be expected to detect the possibility of early lung cancer in a high proportion of cases.

In the past several years a number of mass surveys of relatively homogeneous population groups, involving in one instance almost two million people (Los Angeles), have been carried out and analyzed from the standpoint of lung cancer detection. The screening device used is the photoroentgenogram and the procedure is carried out in mobile or permanent units in a given area. These are then reviewed by panels of radiologists and clinicians, and confirmatory standard films are requested if indicated until the group of lung cancer suspects is isolated. The patients are then referred to existing medical facilities and a group follow-up is maintained to determine eventual outcome. The results of surveys conducted thus far and reported in the literature are contained in Table VI. The results

TABLE VI *

ncidence of Possible Tumors Detected on 14 x 17-in Chest Roentgenograms as a Result of Surveys

Location	No Examined	No of Tumor Suspects	Rates/1000 Persons Examined
Savannah-Chatham Co, Ga	67,961	43	0.6
Gaston & Wayne Cos, N D	84,599	58	0.7
Milwaukee, Wis	176,459	37	0.2
Minneapolis, Minn	301,513	404	1.3
Washington, D C	439,927	373	0.8
Seattle-King Co, Wash	368,129	261	0.7
Tacoma, Wash	72,703	32	0.4
Spokane, Wash	106,526	67	0.6
Salt Lake Area, Utah	162,351	107	0.7
Boston, Mass	536,012	398	0.7
Los Angeles, Calif	1,867,201	3,500	1.9

d after Guiss (5)

of the chest survey at the Strang Cancer Prevention Clinic and the Memorial Center for Cancer and Allied Diseases were presented in the chapter on roentgen diagnosis.

Despite the fact that millions of Americans have participated in mass chest x-ray programs, and despite the fact that at least a dozen of these have been analyzed from the standpoint of possible tumor detection, there is still considerable difference of opinion as to whether or not it is a worthwhile procedure.

Two of the relatively recent, large, and representative surveys are presented for evaluation and comparison in Table VII. McNulty (6)

TABLE VII

RESULTS OF TWO LARGE COMMUNITY CHEST SURVEYS

	Boston	*Los Angeles*
Total surveyed	536 012	1 867 201
Tumor suspects	398	3,500
Primary tumor confirmed	39 *	339
Benign		79
Malignant	39	260
Bronchogenic carcinoma	39	213
Operated	28	113
Resected	22	84
Follow up (3 years)	5 alive and well	24 alive and well
Others	1 lymphosarcoma	34 sarcoma, etc
Case finding (figures rounded)	1 suspect 1350 persons 1 cancer 10 suspects or 1 cancer 13,500 persons	1 suspect 500 persons 1 cancer 14 suspects or 1 cancer 8000 persons

N B Surveys included all ages, both sexes Other factors discussed in text

* Benign tumors not included

reported some rather discouraging information regarding the Boston Survey, whereas the experience of Guss (5a) in Los Angeles was considerably more heartening. A recent paper by the latter author provides a complete analysis (5b).

Furthermore, any evaluation of surveys, such as is represented in Table VII, must take into consideration the following data, much of it indeterminate, which could materially alter the conclusions drawn

	Boston	Los Angeles
No follow-up, refused treatment, etc	51	237
Metastatic pulmonary tumors	19	105
Bronchogenic carcinoma, presumptive	13	
Tumor clinically benign .		295

Boucot (7) has concerned herself with the screening of more compact population groups. She reported that among 16,038 individuals reporting to the central unit of the Philadelphia Tuberculosis and Health Association between April 1950 and February 1951 there were 14 proven cases of *bronchogenic carcinoma (0.1 per cent). She pointed out that 13 of these 14 cases were among the 10,035 white males over 45 years of age,* so that the incidence of confirmed lung cancer in white males over this age was 1.3 per thousand. The resectability rate for these survey-detected cases averaged about 30 per cent, a fact which Boucot attributed, at least partly, to the fact that most of the patients were symptomatic. In fact, among the 77 patients with lung cancer found between January 1947 and January 1953, by two official Philadelphia survey units, only seven were completely asymptomatic.

This investigator has emphasized the need for "over-reading" of survey films in an effort to increase the detection yield and to reduce the number of potential false negatives. She notes that figures purporting to show the survey prevalence of bronchogenic carcinoma will be conservative if a tissue diagnosis is required for case reporting, since a significant number of cases refuse hospitalization or are not hospitalized by their physicians because of obvious inoperability.

Some of the reasons for the disappointing survey results thus far are readily apparent

1. *Age.* Up to two-thirds of the patients included in some of the mass surveys thus far reported have been under the age of 40 years, where lung cancer is a relative rarity.

2 *Sex.* Up to two-thirds of the individuals covered in some surveys have been females who, under present conditions, account for a relatively small proportion of lung cancer cases.

3. The surveys conducted thus far have been in the nature of a "*single shot*" in a population which had never before been x-rayed For this reason, many of the lung cancer cases which were "detected" were relatively far advanced Also, it is obvious that unless such a survey is repeated routinely, lung cancers which have their origin shortly before or after the completion of the survey may *elude detection.*

4 *Delays.* A very obvious common denominator running through the reports of surveys thus far has been the factor of delay in progressing from suspicion to treatment. This has been due mostly to the scope

of the project and to the inherent administrative clinical and follow-up difficulties. A certain amount, however, was due to inertia or resistance on the part of the patients with suspicious lesions—and even of private physicians

5 *Nonsmokers* A fairly sizable number of persons involved in these surveys may be assumed to have been nonsmokers. Many believe that they are not nearly so vulnerable to the development of lung cancer as their smoking cohorts

6 *Presence of symptoms* No specific figures are available on the number of symptomatic patients included in the total of suspected or confirmed lung cancer cases in these surveys, *i e*, how much detection of truly asymptomatic lung cancer was accomplished Boucot's figures cited above indicate that the survey groups are by no means totally asymptomatic Such a situation contributes to a misleading "tumor suspect" yield, but it also accounts in some measure for the disappointing operability, resectability, and survival rates on follow-up.

A periodic survey concentrating on male smokers over forty years of age with vigorous follow-up of suspects would very likely go a long way toward refuting the criticisms of high cost, low yield, and poor salvage rate commonly directed towards surveys reported thus far However, this thesis will lack concrete proof until a model survey of a population group in which all of these factors are controlled, has been undertaken

RECOMMENDATIONS OF LUNG CANCER CONFERENCE

The requirements for a model survey were outlined in the recommendations of the clinical section of Lung Cancer Conference III sponsored by the American Cancer Society and held at Glenburnie, New York, on September 10–11, 1954 After reaffirming its beliefs in the importance of early diagnosis of lung cancer and the capacity of chest x-ray screening programs to accomplish this, the section pointed out the need for pilot studies for further evaluation The following procedures and suggestions were among those recommended to the divisions of the American Cancer Society as the minimum standards of x-ray screening programs

"1 Miniature films are satisfactory as a screening medium for lung cancer

2 A minimum examination should consist of a single P A film

3 Each film should be examined twice Those examining the films should be urged to note carefully minimal changes even though some over-reading may occur

4 The films should be classified negative or positive regardless of the nature of the abnormality observed Those classified as positive merit an interview and a 14 x 17 full sized film as part of the pre-referral process to reduce unnecessary referrals

5. Every positive case should be referred immediately for clinical study and evaluation

6 No case shall be closed until the clinical study is complete

7. For men over 45 the survey film should
and preferably every six
history of smoking, and al
pared with previous films.

8 The original survey film, or a copy, should be sent to the personal physician of *all* participants in the survey *every* time a survey film is taken. This will insure more interested scrutiny as well as comparison of the films with those of the local doctor than present mass reading provides It will also interest and alert the private physician to the importance and potentialities of the program."

The conduct of such surveys is basically a community or public health problem, but the individual physician bears the responsibility of encouraging his patients to participate in these survey programs and of relentlessly pursuing the differential diagnosis of tumor suspects referred to him for evaluation as a result of them. Indifference or even hostility to these surveys on the part of private physicians and delay in determination of final diagnosis of suspects have contributed in large measure to some of the poor results reported.

The Hospital—the Admission Chest Film

The addition of a chest film to the list of routine screening procedures customarily carried out on all hospital admissions has been gaining increasing acceptance in the United States. This relatively simple procedure has been found to add greatly to the completeness of the general work-up of patients and is a natural outgrowth of experience with x-ray surveys for tuberculosis, cancer, and other diseases Since more than twenty million patients are admitted to general hospitals in the United States each year, it is apparent that an appreciable proportion of the population can be screened in this manner This is especially worthwhile, since the expected incidence of abnormal chest x-rays in the hospital population has been estimated to be many times as great as that encountered in a community survey (8).

A recent report (9) has indicated the great increase in the number of hospitals having facilities for routine admission x-rays since 1948, and the percentage of positive case-finding has increased proportionately. For example, in New York State, where 35.7 per cent of the hospitals have such facilities, recent figures demonstrate this graphically (8). In 1953, 254,549 patients, 15 years of age or over, had admission chest films. The rate of pick-up of intrathoracic tumor suspects was as follows·

All Ages	*Rate/1000*
Total	4 4
Male	8 2
Female	2 5

The importance of the selecting factors of age and sex is demonstrated below

Age 45 and Over	*Rate/1000*
Male	13 6
Female	6 9

The authors estimate on the basis of several spot checks that about 10 per cent of these suspects will eventually prove to have bronchogenic carcinoma

In hospitals with 250 patients and over in this country nearly 50 per cent report having facilities for routine chest x-rays of all admissions However, when the smaller hospitals are taken into consideration, a total of only 28 9 per cent of all admissions to general and special short-term hospitals have access to these facilities The variation between states is great In no state does a majority of hospitals report having facilities for routine chest x-rays on admission In four states, more than one-third of the hospitals report that they have such facilities, while in each of six other states the total is less than 10 per cent In conclusion, then, the recent trend is encouraging, but there is still a great deal of progress to be made Several studies have reported on the benefits accruing from the institution of such a program of routine chest films on admission (10, 11, 12, 13) Sweet and Wilkins (14) especially emphasize its importance in patients over middle age

The Private Physician—the Routine Chest Film

The ultimate logical extension of the full utilization of chest x-rays in the detection of lung cancer is the use by the private physician himself of frequent chest x-rays or encouragement of his patients to participate in chest film surveys that are available at no charge It should be underscored here that chest fluoroscopy is not a dependable method for the detection of the relatively minute and subtle changes of early lung cancer, although, in proper hands, it may be of considerable aid once the suspicion has been raised by conventional x-ray films

Whether the patient is an asymptomatic individual with an abnormal survey or routine film, or one with minimal respiratory symptoms, there is need for speed and decisive action on the part of the private physician in the differential diagnosis and management of the lung cancer suspect—*or the patient who should be one* Here the whole spectrum of diagnostic measures is brought into play, including a number of special x-ray

views and techniques, bronchoscopy, cytologic and bacteriologic examinations, skin testing, and finally exploratory thoracotomy. In reviewing the subject of lung cancer detection and diagnosis, one is impressed b the fact that frequently the errors made in bridging the gap between th detection or diagnostic procedure, the creation of suspicion, the establish ment of the diagnosis, and the ultimate management of the patient, are traceable not to a dearth of diagnostic avenues but to their very multiplicity. This observation is particularly applicable with regard to delay in the employment of exploratory thoracotomy in the management of the asymptomatic—or even symptomatic—pulmonary lesion and the so-called "clinically benign" lesion. In the hands of a competent thoracic surgeon this ultimate diagnostic procedure is attended by an entirely acceptable risk of mortality and morbidity.

We believe that discouraging percentages of operability, resectability, and five-year survivals are primarily a reflection of failure to detect carcinoma of the lung in its incipient or earlier stages Factually, this seems to be borne out by surveys such as that of Bloomer and Lindskog (15) who compared three series of one hundred consecutive cases of lung cancer seen in 1938–1943, 1943–1946, and 1947–1949. There was no difference in the time elapsing between the onset of symptoms and the institution of investigation and treatment among the three groups. A similar opinion was voiced by Stranahan, Ehler, and Olson (16). These discouraging figures are probably due to a combination of delay by the patient in seeking his doctor's advice dela[illegible] ng suspicio[illegible] uspects [illegible] ow avai[illegible] community, hospital, and private practice level for the [illegible] application of the techniques etection of lung cancer.

There appears to be some evidence that carcinoma of the lung detected

TABLE VIII *

COMPARISON OF SURGICAL RESULTS IN SURVEY vs NON-SURVEY LUNG CANCER

Cases	Survey Carcinoma	Non-Survey Carcinoma
Total number	30	263
Explored	26 (87%)	168 (64%)
Resected	23 (77%)	100 (38%)
No pathologic evidence metastases	13 (57%)	40 (40%)
Three-year survivors	9 (30%)	32 (12%)

* [Modi]fied after Overholt and Bougas (19).

by survey techniques, particularly when in the "silent phase," has a significantly higher operability and five-year survival rate (17, 18). Table VIII summarizes the experience of the Overholt Thoracic Clinic. Sixteen additional patients with lung cancer detected by survey have recently been added, of whom ten are living more than one year after operation. These encouraging results were recorded despite the fact that 18 (39 per cent) of the entire group of 46 developed symptoms during the six months elapsing between detection by survey and operation.

The opportunities and responsibilities of the private physician in the detection and early diagnosis of lung cancer can be tabulated in stepwise and somewhat arbitrary fashion as in Table IX.

Just as the detection of unsuspected pulmonary neoplasms was originally a by-product of surveys conducted for the detection of tuberculosis, so also it is reasonable to anticipate unexpected dividends in the form of *other asymptomatic chest pathology* in the process of screening for lung cancer. This includes not only benign neoplasms but also cardiac and mediastinal abnormalities.

SUMMARY

The ultimate goal of efforts directed toward control of lung cancer is the development of practical measures of prevention. However, achievement of the maximum degree of detection of presymptomatic—and thus potentially curable—lung cancer depends upon the proper utilization of keen clinical judgment and experienced x-ray interpretation.

It is true that the routine or survey chest x-ray is by no means the solution to the problem in which current statistics on detection, early diagnosis, and cure are so discouraging. However, it seems entirely likely that if the simple measure of a chest x-ray, as typified by the mass survey, the hospital admission film, and the routine chest x-ray in private practice, were intelligently exploited to the utmost, an encouraging yield of early, curable cases could be brought to the surgeon.

Such a program can be a practical reality only if several criteria are met in selecting persons for periodic study, such as that of specially encompassing smoking males of 40 or more years of age. Also inherent in the concept of such a program is its annual or semi-annual repetition, and rapid and complete evaluation of tumor suspects.

Experience to date with representative mass chest x-ray surveys has been briefly reviewed and reasons cited for the variable and sometimes disappointing results recorded. The benefits of routine chest x-rays on all hospital admissions and patients seen by the private practitioner, especially in the older age groups, have been stressed.

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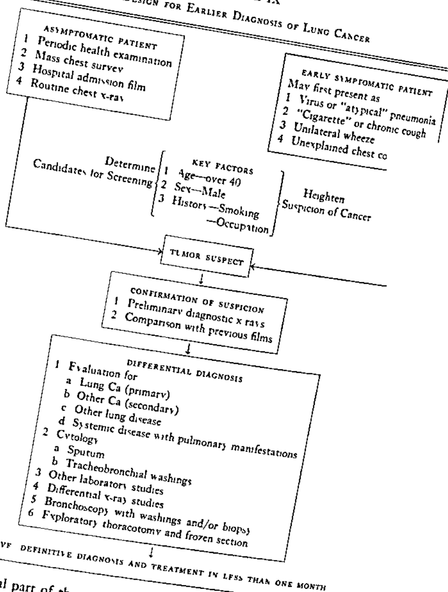
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TABLE IX

DESIGN FOR EARLIER DIAGNOSIS OF LUNG CANCER



An integral part of this program is the concept of early detection and the aggressive confirmation or rejection of the suspicion of lung cancer once it has been raised, either by a routine chest film or by minimal symptoms The pivotal role played by the private physician in this stage of the process has been underlined and a suggested approach to the problem set forth

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10

The Differential Diagnostic Aspects

Edgar Mayer and Israel Rappaport *

Errors in diagnosis are most likely to be made in the early phase of pulmonary cancer when the signs and symptoms are minimal and, not infrequently, intermittent. When the diagnosis is doubtful, it is better to err on the safe side by considering the lesion as malignant. Therefore, it is an accepted principle that when such doubt exists an exploratory thoracotomy is indicated, and not prolonged observation. The problem is especially urgent when there is a manifest pulmonary lesion that has already passed the initial phase.

The differential diagnosis of lung cancer includes a consideration of all types of pulmonary disease, many mediastinal processes, and at times cardiac or even chest wall and diaphragmatic abnormalities. The most common and most important pulmonary diseases can best be considered from the point of view of differential diagnosis under three headings:

a) The pulmonary processes that frequently simulate lung cancer by association, such as *bronchitis, pneumonitis, and tuberculosis.*

b) The solitary pulmonary lesions with a roentgen appearance suggestive of lung cancer, the so-called "*circumscribed solitary lesions*" of which there are a great variety both of inflammatory and of neoplastic origin.

c) Miscellaneous diseases which may resemble lung cancer because of their endobronchial, hilar, or mediastinal location, such as *endobronchial granulomas, benign bronchial tumors, hilar lymphadenopathy,* and certain *mediastinal neoplasms.*

* Grateful acknowledgment is made to Drs. Herbert C. Maier and John LaDue for helpful suggestions in the preparation of this chapter and for several illustrative x-rays.

1 ASSOCIATED PULMONARY PROCESSES

Bronchitis The bronchitis accompanying bronchogenic carcinoma is often of a localized obstructive type, first manifesting itself by a localized intermittent wheeze which later becomes more constant Occasionally bronchitis may accompany the new growth as a generalized form, especially among heavy smokers, and may thereby mask the neoplasm itself

Pneumonitis In preceding chapters it has been emphasized that pneumonitis develops frequently in lung areas peripheral to bronchogenic cancer, and that in a large proportion of cases the first clinical manifestations of the neoplasm are those of obstructive pneumonitis So common is this association that it has been widely considered as the most serious stumbling block to early diagnosis In approximately 85 per cent of pulmonary cancers the resected lungs show evidence of chronic inflammatory changes The fact that cancer may masquerade under the guise of a lung infection has been emphasized so much that the present trend in some clinics is to overlook even the possibility of the existence of a simple pneumonitis It has now become necessary to point out the fact that chronic pneumonitis may also simulate lung cancer In the cancer age-group, delayed resolution of acute bronchopulmonary infections leading to chronic processes is not infrequent Also in recent years, forms of slowly resolving pneumonias of viral origin and of so-called atypical pneumonias have become frequent clinical phenomena All of these now frequently raise the suspicion of lung cancer Many pulmonary resections have been and are being carried out for suspected cancer in cases where the lesions resected prove to be merely chronic infectious processes.

The clinical picture does not necessarily afford the means of differentiation between obstructive pneumonitis due to cancer and that arising from benign etiology This is especially true of the chronic pneumonitis associated with extensive cholesterol deposits Protracted low grade fever, cough, expectoration, leucocytosis and elevated sedimentation rate, may point to an uncomplicated inflammatory lesion, but even positive bacteriologic findings will not conclusively settle the diagnosis, inasmuch as all of these findings often exist in pneumonitis due to malignant bronchial obstruction Persistent localized wheeze, if present, is one clinical feature to which greater significance can be attached under these circumstances (Fig 111) Pneumonitis that does not completely clear on the roentgenogram with adequate chemotherapy, as well as repeated attacks of pneumonitis, should make one suspicious of carcinoma

Bronchoscopy may be an important differential diagnostic procedure The finding of rather diffuse chronic inflammatory changes in the central

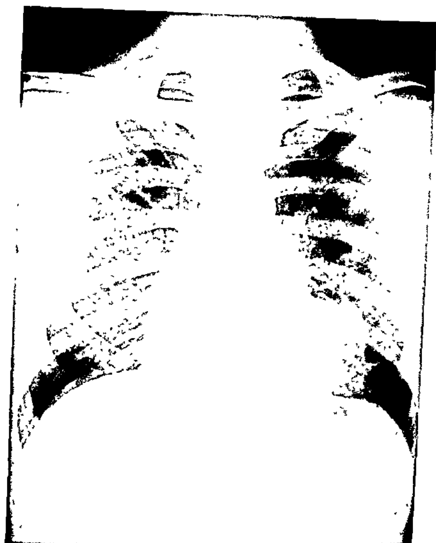


Fig 111 Area of pneumonitis in lingular portion of left upper lobe such as may be seen with either chronic interstitial pneumonitis or pneumonitis secondary to carcinoma

bronchi and especially in the trachea points toward an inflammatory process. Patients with pneumonitis whose central bronchi are clear by [illegible] the [illegible]osis, provided [illegible] pneumonitis to be differentiated from lung cancer is tuberculosis Not only does tuberculosis commonly coexist with pulmonary cancer but it is often indistinguishable clinically

Coexistent tuberculosis is a not uncommon and a difficult problem in the differential diagnosis of lung cancer In approximately 10 per cent of all lung cancers, tuberculous lesions are coexistent Except for the rare instances in which a necrotic cancer opens up a dormant old closed tuberculous lesion, the association is quite coincidental It is brought about by the peculiar circumstance that tuberculosis and lung cancer predominantly affect middle-aged men The epidemiologic peak of tuberculosis in men has in the last generation shifted to middle age and is now most common in men of 45 to 54 years of age It has been repeatedly emphasized that during the same period the incidence of lung cancer has risen tenfold in the same age group It is therefore not surprising that coexisting pulmonary tuberculosis and cancer are not uncommonly observed in middle-aged men Therefore it is clinically important to rule out carcinoma of the lung in patients of cancer age with an established diagnosis of tuberculosis (positive sputum), bearing in mind the possible coexistence of the two diseases

Recognition of this coexistence in the operable stage of lung cancer calls for acute clinical acumen based on extensive clinical experience and on thorough individualized diagnostic study Most symptoms, especially cough, hemoptysis, chest pain, and weight loss are common to both diseases, however, certain differences exist that may point toward a correct diagnosis For example, cough out of proportion to the amount of sputum produced is more consistent with bronchogenic cancer, hemoptysis is apt to be more profuse in tuberculosis and is usually followed by expectoration of sputum containing tubercle bacilli, and persistently negative sputa favor a diagnosis of neoplasm Chest pain in cancer is more sharply localized and has a dull and persistent character, while pleuritic pain in tuberculosis is apt to be transient, more intense, and aggravated by deep breathing Loss of weight in tuberculosis is apt to come on much earlier

Obstructive bronchial tuberculosis with or without secondary infection may simulate bronchogenic cancer so closely that differentiation may

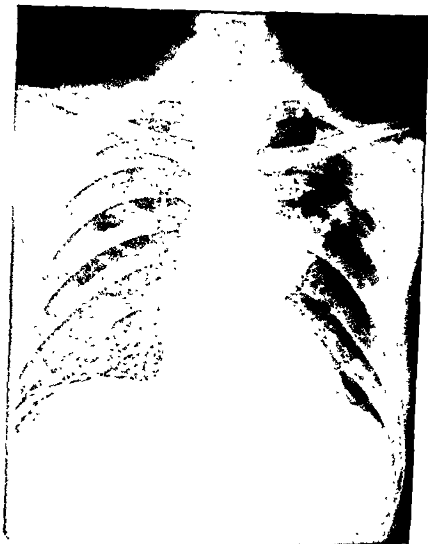


Fig 112 Roentgenogram of an elderly male who had a negative x-ray one year previously Preoperative diagnosis was bronchogenic carcinoma but localized tuberculosis was found at operation

only be possible by biopsy (Fig 112). Tuberculosis of the bronchi is more common in females, in whom cancer is relatively less frequent. In males of cancer age this clinical picture simulating bronchogenic new growth is at times due to tuberculous broncholiths at the roots of the lungs from involvement of adjacent lymph nodes Sputum persistently positive for tuberculosis but negative for cancer cells usually establishes the correct diagnosis The diagnosis has occasionally been made possible by the use of antibiotics but valuable time may be lost by this means Absence of response to antituberculosis drugs or increase in the size of lesions despite their use suggests the presence of carcinoma of the lung although this can be deceptive and should not be relied upon too greatly.

Tuberculosis in the form of tuberculoma is difficult to differentiate from pulmonary cancer and will be discussed under "solitary circumscribed pulmonary lesions"

All these diagnostic means often remain inconclusive for too long a period of time Therefore when suspicion of cancer persists, exploratory surgery is all the more justified because resection is also the indicated treatment for tuberculomas and tuberculous bronchial processes associated with secondary inflammatory disease

2 SIMULATION OF LUNG CANCER BY ROENTGEN FEATURES

The role of the x-ray survey for detection of early lung cancer has been evaluated in a previous chapter Certainly the roentgenogram has assumed great clinical importance in differential diagnosis Traditionally the "*solitary circumscribed lesion*" is the one most widely associated with the concept of lung tumor Routine survey chest x-rays of symptom-free individuals taken in periodic health examinations in the search for tuberculosis, and more recently for lung cancer, have brought to light many lesions of varied etiology but with one feature in common, namely, their solitary circumscribed appearance The fact that large numbers of such lesions have been so discovered, thoroughly studied clinically, and classified histologically after resection, greatly enhances their clinical importance

Experience has shown that practically every conceivable intrapulmonary, endobronchial, and intrathoracic disease can at times appear in the form of a solitary circumscribed lesion and that the differentiation of these encompasses the whole broad field of differential diagnosis of chest diseases (Fig 113) The tabulation quoted below from a presentation of recent date is most instructive regarding practical experience with lesions discovered on roentgenograms in apparently symptom-free indi-

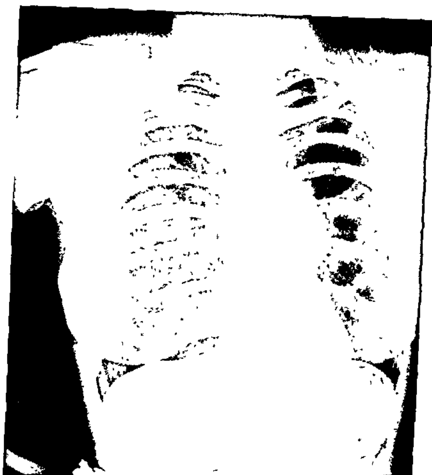


Fig 113 Woman with hemoptysis as presenting symptom Negative x-ray two years previously Preoperative diagnosis "tumor." Operation revealed a large blood clot *within a pulmonary cyst.*

viduals It also casts an illuminating light on the practical problem of differential diagnosis

Malignant tumors, not found in this series, include sarcoma, neurogenic sarcoma, neurofibrosarcoma, and lymphoblastoma. *The benign tumors* not included are mesothelioma, dermoid cyst, thymoma, intercostal *neuroma, and unclassified benign lesions More than* one-quarter of these lesions are bronchogenic cancers, and if other malignant neoplasms are added, the proportion of malignancies include more than one-third of the total Inflammatory processes make up the largest proportion (40 per cent) of circumscribed solitary lesions in this particular study. One-quarter of the lesions consist of benign tumors and miscellaneous diseases which at times may become dangerous through complications.

TABLE X

714 HISTOLOGICALLY PROVED CASES OF ISOLATED CIRCUMSCRIBED LESIONS OF THE LUNG *

Malignant tumors	225 (35.8%)
Benign tumors	89 (12.5%)
Inflammatory lesions	284 (40%)
Miscellaneous	86 (12.5%)
	714 (100%)

Malignant tumors include		*Benign tumors*	
Primary bronchogenic cancer	190 (26.6%)	Hamartoma	57 (0.8%)
Bronchial adenoma	25 (3.5%)	Fibroma	10 (1.4%)
Lymphosarcoma	10 (1.4%)	Chondroma	5 (0.7%)
Malignant metastases	20 (4.2%)	Hemangioma	17 (2.2%)
Inflammatory lesions		*Miscellaneous*	
Tuberculoma	104 (14.6%)	Bronchial cyst	39 (5.5%)
Granuloma undetermined type	135 (19%)	Unclassified	25 (3.5%)
		A-V aneurysm	2 (0.2%)
Coccidioidal granuloma	3 (0.4%)	Pericardial cyst	2 (0.2%)
Chronic pneumonitis	28 (3.9%)	Broncholithiasis	5 (0.7%)
Chronic abscess	6 (0.8%)	Diaphragmatic hernia	7 (1.0%)
Empyema	3 (0.4%)	Liver abscess	2 (0.2%)
Actinomycosis	1 (0.1%)	Aortic aneurysm	1 (0.1%)
Echinococcus cyst	2 (0.2%)	Mediastinal cyst	1 (0.1%)
Lipoid pneumonia	1 (0.1%)	Gastric cyst	1 (0.1%)
Bronchiectatic cyst	1 (0.1%)	Hematoma	1 (0.1%)

* Excerpted from Jones, R. C., and Cleve, E. A.: "Solitary Circumscribed Lesions of the Lung. Selection of Cases for Diagnostic Thoracotomy," *A. M. A. Arch. Int. Med.*, 93:842-849, 1954.

Current discussions of isolated circumscribed lesions emphasize that differentiation by available clinical diagnostic methods is very difficult. As practically all of these lesions have been x-ray discoveries in symptom-free individuals, both the history and the physical findings were essentially without differential diagnostic value, except for the *age factor*. The age of patients in the above-quoted study ranged from the second to the seventh decades. Since carcinoma of the lung is rare under the age of 35, a higher percentage of these lesions is found to be carcinomas when an older age group is studied. Over 50 years of age, the majority of circumscribed pulmonary lesions may be cancer.

The roentgenographic features of "coin" lesions have been fully discussed in a previous chapter on x-ray diagnosis. However, the size, shape, and definition of a lesion on the roentgenogram will not identify its character in the lungs. An unchanged appearance for long periods sug-

gests a benign process but does not exclude malignancy, because some cancers have been observed to remain unchanged for months and even for a few years. On the other hand benign lesions (tuberculosis, mycoses and cysts) frequently become larger under observation. *Calcification* in round lesions is generally considered as evidence against malignancy. However, instances of malignant tumor developing about old calcific deposits, as well as cases of deposits of calcium within malignancies, have been reported. Calcification within solitary circumscribed nodules occurs in old tuberculous foci, in granulomas such as histoplasmosis and coccidioimycosis, in hematomas, hamartomas, and in a few other conditions. Some calcified tuberculous lesions yield positive cultures of tubercle bacilli but laminated lesions are generally sterile. Lamination practically never occurs in tumor.

Other measures for differentiating circumscribed solitary lesions must be considered *Skin tests* for tuberculosis and mycoses have limited value. A negative tuberculin reaction may increase the index of suspicion of malignancy, and positive tests for mycoses (coccidioidin, histoplasmin) may raise suspicion of the latter especially if accompanied by a positive complement fixation test of high titer. They rarely however actually identify the etiology of a round lesion.

Bronchoscopy has not been helpful in these cases as the lesion is beyond the accessible range of visibility. However, bronchial washings may at times be positive for cancer cells Needle aspiration of such lesions is not recommended.

One type of "coin" lesion is the tuberculoma which consists of a mass of conglomerate tubercles with varying amounts of caseation, and is one of the lesions of chronic pulmonary tuberculosis. It occurs frequently as the only demonstrable tuberculous lesion in the lung, either single or multiple (Fig 114) Tuberculomas may appear anywhere but they are most frequent in the upper parts of the lungs, varying in size from that of a small pea to that of a large walnut They may persist unchanged for many years and then caseate and break down, or they may go on to calcification which becomes evident in the x-ray as small punctate calcium densities or as concentric lamination within the round opacity. (By the use of the acid-Schiff stain, some of the resected so-called tuberculomas have been shown to be lesions of histoplasmosis Indolent mycotic foci must always be borne in mind.)

Metastatic neoplasms in the lungs from cancers of other organs appear occasionally as solitary nodules although they are frequently multiple or may multiply while under observation Metastases from cancers elsewhere in the respiratory tract (bronchus, larynx, and lungs) are not rarities. Pulmonary metastases are commonly associated with metastases to other organs It is therefore important to search for not only the

primary tumor, but also for other metastases A history of a previous or simultaneous malignancy should strongly suggest the malignant nature of the pulmonary lesion In some instances the primary extrapulmonary

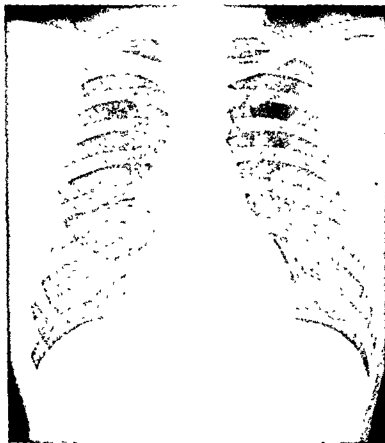


Fig 114 Coin lesion near anterior end of third right rib was a typical tuberculoma

growth may have been removed many years earlier. Local respiratory symptoms are not a prominent feature although cough and dyspnea are not uncommon On the other hand hemoptysis or expectoration is relatively uncommon in metastatic growths in the lungs

Benign tumors presenting themselves as solitary circumscribed lesions in the pulmonary parenchyma are rare and are considered in a special chapter Their positive diagnosis is generally not established prior to

surgery, with the exception of hemangioma. They rarely obstruct large bronchi or cause obstructive symptoms These tumors may cause nonproductive cough but chest pain and hemoptysis are uncommon The clinical picture is not characteristic except that *hemangioma or pulmonary arteriovenous fistula* may simulate congenital cardiac disease with clinical signs of cyanosis, polycythemia, and clubbed fingers and toes. Severe hemoptysis may be a prominent feature of hemangioma The diagnosis may be definitely established by angiocardiography. A murmur which may be systolic or continuous is not infrequently heard over the site of the lesion

Pulmonary infarction may at times be confused with bronchogenic neoplasm, especially if it is not borne in mind. It may occur in the ambulatory patient, often as the result of silent thrombosis of the veins of the lower limbs. Its shape on the roentgenogram is not necessarily triangular *with the apex toward the heart, in fact it is more apt to be oval or triangular* with the apex toward the periphery, and radiologically it may mimic almost any lung disease. A history of sudden chest pain and dyspnea followed by hemoptysis is most characteristic, but is often absent

Pleural mesothelioma, an unusual tumor and not truly intrapulmonary, should be referred to here because it has been wrongly diagnosed as bronchogenic carcinoma It can appear radiographically as a solitary isolated lesion and is commonly *accompanied by arthritis and digital* clubbing Pleural tumors are discussed at greater length in a special chapter

Conglomerate silicosis is included merely because on rare occasion it has been misdiagnosed as bronchogenic carcinoma In such instances the smaller silicotic nodules were not detectable because of the accompanying emphysema

Hydatid cysts may appear as sharply delineated intrapulmonary densities. Skin tests may aid in differentiation

Lipoid pneumonia, due to the aspiration of mineral oil or oily nose drops into the lungs over a long period of time, may mimic cancer of the lung to a marked degree Although this chronic fibrotic pneumonitis may at times be radiologically detectable in the bases of both lungs, it is surprising how often the lesion is apparently localized and therefore simulates a tumor mass. Even localized areas of upper lobes may be the site of the lesion The diagnosis of lipoid pneumonia can be suspected when a history of the use of mineral oil or oily nose drops is obtained, and oil droplets are demonstrated in the sputum or bronchial secretions The surgeon may be unable to differentiate chronic *lipoid pneumonia* from a pulmonary neoplasm on gross inspection at the time of thoracotomy (Fig. 115)

Bronchiectatic or bronchogenic cyst of the lung may appear as a circumscribed lesion. If there is little or no adjacent bronchiectasis, and the cyst does not freely communicate with a bronchus, the lesion may be

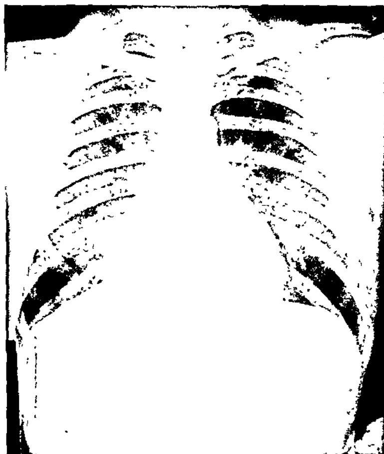


Fig 115 Density at base of right lung was considered to be due to carcinoma both preoperatively and at operation Diagnosis of lipoid pneumonia was established subsequently

asymptomatic At times there is a history of frequent respiratory infections (Figs 116A, 116B).

Mucoid impaction of the bronchi may occur in asthmatics The bronchial obstruction thus produced may lead to an area of pulmonary infiltration which simulates a neoplastic mass on the roentgenogram

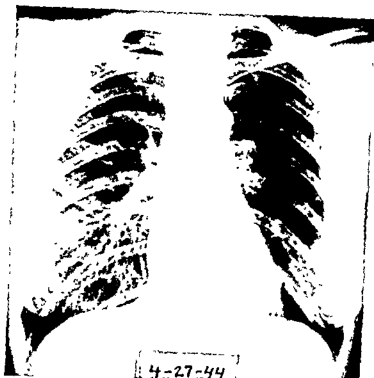


Fig 116A Density in right lung field had been considered elsewhere to be a carcinoma on the basis of a supposedly positive cytologic examination

Hodgkin's disease may produce an intrapulmonary circumscribed density but usually the hilar and mediastinal lymphadenopathy is the prominent feature on the roentgenogram (Fig. 117).

Localized fungus infections of the lung such as coccidioidomycosis, histoplasmosis, actinomycosis, and blastomycosis have also at times been considered as primary pulmonary tumors when they have occurred as circumscribed pulmonary x-rays shadows. Coccidioidomycosis and histoplasmosis frequently occur without pulmonary complaints Diagnosis in many such cases has been suggested by positive skin tests to coccidioidin or histoplasmin. Generally however the diagnosis has not been made clinically but has been established only by exploratory thoracotomy

Actinomycosis and blastomycosis usually present pulmonary or systemic symptoms unless the lesion is small and localized The usual doses of antibiotics may limit the tendency of the infection to spread without eradicating the process Thus it is now more common to have the lesion simulate a neoplasm than years ago. The demonstration of the fungus in the bronchial secretion suggests the diagnosis but it is important to bear in mind that fungi may be present as secondary invaders and not

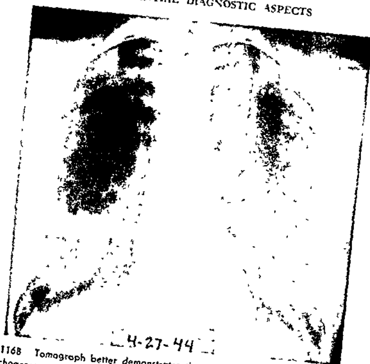


Fig 1168 Tomograph better demonstrates the contour of the lesion which was a bronchogenic cyst.

be responsible for the pulmonary lesion under question Exploratory thoracotomy together with large doses of antibiotics is indicated for diagnosis and therapy (see Fig 123)

Circumscribed solitary lesions with cavitation present the problem of differential diagnosis between broken-down tuberculoma, necrotic cancer, frank lung abscess, and abscess secondary to obstructing carcinoma This diagnosis at times offers great difficulties As pointed out in the chapter on pathology, frank abscess behind an obstructing bronchial cancer is now relatively rare and is usually the result of necrosis of cancer tissue rather than the necrosis of infected lung tissue Frank lung abscesses are usually seen in the mid-lung fields posteriorly, namely, the lower parts of the upper and the upper parts of the lower lobes Carcinomatous "abscesses" may appear anywhere in the lungs as one or several small cavities within a large opacity, or as a large cavity with a wall of varying thickness, or the cavity may occupy an eccentric position within the lung density The patients are predominantly males who are free of the clinical features usually associated with simple abscess Careful study of the sputum of such patients almost always reveals cancer cells. The differenti-

bility by surgery is practically the rule. Nevertheless the clinical picture of bronchial adenoma is much like that of bronchogenic cancer. Obstruc-

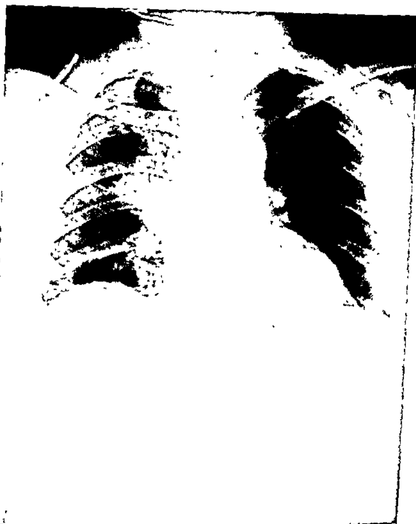


Fig 118 Roentgen findings of bronchostenosis in this 49-year-old male suggested carcinoma, but the history of several pneumonias over a 20-year period pointed to a lesion of long standing Operation demonstrated bronchiectasis secondary to bronchial erosion by a calcified lymph node

tion of bronchi as in cancer leads to suppurative disease which may eventually result in destruction of part or all of the affected lobes or lungs However, the differential diagnosis is usually not difficult, since bronchial adenoma is more apt to develop in young women in contrast to the fact

that middle-aged men with bronchogenic cancer outnumber the women by six to one. Hemorrhages are often more protracted and profuse with bronchial adenoma and cough is more apt to be productive of massive amounts of sputum with each recurrent attack of suppuration.

Conclusive diagnosis of bronchial adenoma is usually made by bronchoscopy and experienced bronchoscopists can often recognize the lesion on sight. It is almost always found in a primary bronchus or close enough to permit visualization by bronchoscopy, and it tends to bleed profusely on biopsy. Some of the tumors are pedunculated and have been removed by the bronchoscopist. However, most surgeons feel that removal at thoracotomy is indicated. The differential diagnosis of adenoma and bronchogenic cancer was formerly more of academic than of practical interest because of their clinical similarity as well as the need for pulmonary resection in both. However, this is no longer the case since recently perfected bronchoplastic procedures permit wide excision of tumors invading structures of the bronchial wall without the sacrifice of whole lobe or lung.

Hilar lymphadenopathy may produce symptoms of bronchial irritation and compression as seen with endobronchial tumors. Moreover, the roentgen appearance may simulate that of a neoplastic mass in the hilar region of the lung. Such lymphadenopathy may be caused by a wide variety of processes such as tuberculosis, Hodgkin's disease, various other granulomatous lesions, lymphosarcoma, sarcoidosis, silicosis, etc. When the hilar enlargement is bilateral, confusion with bronchogenic carcinoma is less likely to occur, but an anaplastic cancer of the lung may occasionally be accompanied by bilateral hilar metastases. If the mass on the x-ray is located by lateral film in the hilar region, appears nodular or scalloped, and does not conform to a bronchopulmonary segment, hilar lymphadenopathy is a good possibility if bronchoscopic examination shows no endobronchial tumor. The presence or absence of other roentgen shadows in the lung fields may aid in differentiation. Scalene node biopsy is often diagnostic. Exploratory thoracotomy is necessary in some cases.

Mediastinal tumors. This collective term is now used for a large group of masses having a common anatomical site. This includes not only a great variety of diseases (inflammatory, neoplastic, and others) of the structures of the mediastinum itself, but also processes that extend into it from bordering structures. Accordingly bronchogenic cancers often come under this category. Bronchogenic cancers extending rapidly to hilar and mediastinal structures present at first as masses merging with the central mediastinal shadow. In fact they are the most common malignant lesion originating within the chest involving the mediastinum. As such they often present the problem of differentiation from other

mediastinal masses, of which there is such a large variety (Fig. 119). Even the briefest discussion would go far beyond our scope here. Therefore we will limit our remarks to the general principles of differential diagnosis of mediastinal masses

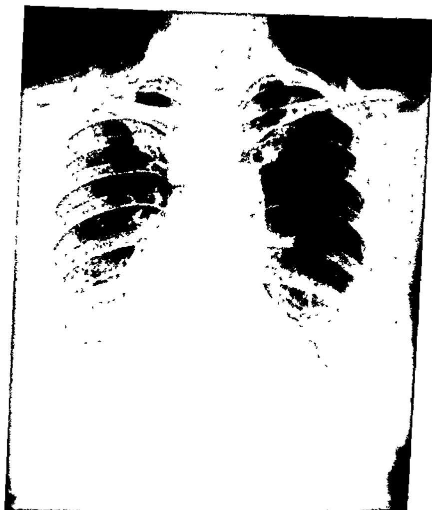


Fig 119 Paramediastinal mass in this 66-year-old male with complaint of cough revealed itself on operation to be a resectable mediastinal lymphosarcoma without pulmonary involvement

Many mediastinal tumors are first discovered accidentally by x-ray, as they are frequently asymptomatic The symptoms and signs relate to the location of the mass, its invasiveness, and the presence or absence of secondary infection, as well as to special metabolic effects of some tumors.

The location of the mass in relation to the tracheobronchial tree determines the time of onset and type of respiratory symptoms. A slowly growing mass in the anterior mediastinum may attain a huge size without causing symptoms whereas a small tumor adjacent to the trachea or bronchi causes early symptoms because of pressure on these structures. Such symptoms include dyspnea of varying degree, wheezing, transient or persistent, and cough, especially on change of position. Infection will result in purulent or bloody expectoration. Chest pain is relatively mild with most mediastinal tumors, while constant boring pain is indicative of invasiveness.

The physical findings may be negligible or striking. Pressure on the superior vena cava may result in marked dilation of the veins of the head and neck and anterior thorax, fullness at the base of the neck, and puffiness of the face on arising. Metastatic adenopathy may be present in the neck. Percussion may uncover widening of the mediastinum, on auscultation wheezing suggests bronchial compression, and thrills or murmurs suggest pressure on vascular structures. Fluoroscopy gives valuable information about the location of the mass and its relationship to adjacent structures. Expansile pulsation suggests a vascular lesion, although some pulsating mediastinal masses will prove to be tumors, some of which can be resected. The degree of pulsation of a mass does not tell whether it is a vascular or cystic tumor. When there is doubt, angiograms may clear up the uncertainty. Movement with respiration suggests pulmonary origin, movement with swallowing suggests esophageal involvement (Fig. 120). Paralysis of the diaphragm usually indicates an invasive tumor.

X-ray studies afford more exact information as to location of the mass. This can be determined exactly with multiple exposures, namely, oblique and lateral projections from both sides, with standard or penetrating (Bucky grid) exposures. At times sectional (tomographic) x-ray films must be resorted to for exact localization. Most tumors have a predilection for specific mediastinal locations.

Tumors of the anterior mediastinum include substernal thyroid, thymic tumors, teratomas, cysts, and tumors of the pericardium and heart. In the middle and posterior mediastinum, aneurysms, bronchogenic cysts, metastatic neoplasms, and granulomatous and lymphatic lesions including the lymphomas, tuberculosis, and sarcoidosis are characteristically found. Sometimes esophageal tumors may lead to confusion. The costovertebral area is the site of preference for neurogenic tumors.

The methods of study for differential diagnosis include angiography, bronchography, metabolic and bone marrow study, and finally biopsy. Angiography usually defines mediastinal masses of vascular origin. Bronchoscopy will help to exclude lesions arising in the bronchi, as well as indicating extrinsic pressure. Substernal goiter may be associated with



Fig. 120 Roentgenogram of 71-year-old woman with dyspnea Pulmonary carcinoma, previously suspected, was ruled out by noting movement of the mass with swallowing Operation revealed a bronchogenic cyst of the mediastinum

changes in the metabolic rate A radio-iodine "pickup" will usually define a substernal goiter. The presence of myasthenia gravis usually suggests that the mediastinal tumor is thymic in origin Biopsy of enlarged lymph nodes in other areas will often permit the diagnosis of lymphoma or sarcoidosis. Exploration of cervical tissues in the area of the scaleni is often indicated Studies of the peripheral blood and bone marrow may reveal the presence of lymphatic leukemia as a cause of the mediastinal enlargement Careful study of the patient as a whole may reveal that the mediastinal enlargement is due to metastatic tumor from a distant primary source. In the patient in whom lymphoma is suspected, irradiation of

the mediastinum may result in rapid disappearance which will permit a tentative diagnosis In view of the importance of an accurate histologic diagnosis, however, we prefer exploratory thoracotomy when diagnosis cannot be made by any other means

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11

Functional Aspects of Pulmonary Disease as Applied to the Management of Cancer of the Lungs

ISRAEL RAPPAPORT
AND HERBERT C. MAIER

It is hardly necessary to point out that an understanding of lung function and dysfunction better enables us to interpret the clinical features of pulmonary diseases, and is therefore helpful in their treatment. Assessment of lung function by recently elaborated tests is coming into ever wider use. In the case of bronchogenic cancer this is true perhaps to a somewhat more limited extent than to most other pulmonary diseases, because the lethal potentialities of cancer do not permit the same regard to preservation of lung function as is desirable in the management of nonmalignant lesions. Yet it may truly be said that even in this disease appreciation of the functional aspects to be discussed here is essential to the full mastery of clinical management. For the discussion of pulmonary dysfunction it is necessary to provide background information regarding the major aspects of pulmonary function and the methods now used for the assessment of their efficiency.

ORGANIZATION OF PULMONARY FUNCTION

The primary function of the lungs is the exchange of the respiratory gases—oxygen and carbon dioxide. The transfer of these gases is by diffusion. This physicochemical process takes place over the surface of contact between the gas in the alveoli and blood in the capillaries, due to differences in partial pressure. The air and blood supply of the alveoli is dependent upon the breathing activity of the chest and the blood-pumping activity of the heart. However, normal gas exchange is dependent directly upon local adaptation of ventilation, blood flow, and

diffusing surface in the alveoli. There is now reason to believe that this functional adaptation at the alveolar level is accomplished somewhat independently from ventilation and circulation in the lungs as a whole. Pulmonary function is under constant regulation by the homeostatic mechanisms of the body in response to changing metabolic requirements.

Pulmonary function thus comprises four distinct components, each of which is interrelated with the others.

1. *Breathing* is performed by the bellows action of the chest. It is concerned with the maintenance of lung volumes, their constant refreshment (pulmonary ventilation), and with the work performed by the mechanism of breathing.

2. *The pulmonary circulation* is propelled by the pumping action of the heart. It is concerned chiefly with maintenance of blood flow and pressure conditions in the pulmonary vascular bed optimal for normal function of the lungs and heart.

3. *Gas exchange* phenomena are concerned with maintenance of normal levels (pressures and contents) of the respiratory gases in the arterialized blood leaving the lungs through the pulmonary veins. This includes the physicochemical criteria for transfer of the gases in the alveoli and the adaptation of ventilation, blood flow, and diffusion surface at the alveolar level.

4. *Regulation of pulmonary function* is concerned with the phenomena of homeostatic control of the correlated functions of gas exchange and breathing from the respiratory center, which involves also the regulation of the acid-base balance of the body.

Analysis of pulmonary function in disease rests on the use of methods for testing the efficiency of these component functions, as follows.

Breathing and its component functions are studied by spirometric methods. Spirometry has become the most useful and versatile tool in the study of pulmonary function. It enables us to measure the movable volumes of air in the lungs (vital capacity and its components). It affords exact measurement of ventilatory capacity, i.e., of the amounts of air turnover. Spirometry enables us to determine O_2 intake and CO_2 output which, when related to the amount of air turned over, affords a measure of utilization of ventilation. Spirometry supplemented by timing apparatus enables us to test the mechanical efficiency of breathing. Last but not least spirometry supplemented with ergometric methods enables us to measure the work expenditure of breathing.

The *pulmonary circulation* is studied mostly by indirect methods. [A]nalysis of the gases in the arterial blood, when related to data of O_2 [in]take and CO_2 output in the lungs, affords information on rate of blood [flo]w through the lungs. By catheterization of the heart and pulmonary

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artery it is now possible to determine directly the pressure level prevailing *in most of* the pulmonary vascular bed.

Gas exchange efficiency is tested by *gas analytical methods* and is expressed in terms of *O_2 saturation and CO_2 content of arterial blood*, as well as in terms of gradients of tension of these gases in arterial blood and in the alveolar gases

Correlation of the data on pulmonary ventilation and gas exchange enables us to assess *efficiency of ventilation and of circulation at the alveolar level* in terms of gas exchange and in terms of *diffusing capacity* at rest and *maximal diffusing capacity* in exercise

Correlation of the above data with the momentary acid-base balance of the body affords information about the *sensitivity of the respiratory center* and its efficiency in the regulation of pulmonary function.

In explanation of the foregoing, a brief discussion of each of the four components of pulmonary function and their phenomena is here in place.

I Breathing

Breathing is a mechanical process performed by the chest bellows operating through the force of tonic contractions of muscles associated with the chest wall and diaphragm, and the force of "elastic recoil" generated in the elastic structures (in the lungs and chest) during their distended state Breathing operates with a reservoir of gas in the lungs and in cycles of *expansion and retraction by which the air in the lungs is ventilated* In evaluation of breathing we are concerned therefore with the following three components lung volumes, pulmonary ventilation, and mechanics of breathing.

A *Lung volumes and capacities* (adapted from Comroe)

Primary volumes which do not overlap are the following.

Tidal volume is the volume of gas inspired or expired during each respiratory cycle

Inspiratory reserve volume is the maximal amount of air that can be inspired from the end-inspiratory position

Expiratory reserve volume is the maximal volume of gas that can be expired from the end-expiratory level

Residual volume is the volume of gas remaining in the lungs at the end of a maximal expiration

Capacities include two or more primary volumes, as follows

Total lung capacity refers to the amount of gas in the lungs at the end of maximal inspiration

Vital capacity is the maximal volume of gas that can be expelled from the lung by forceful effort following a maximal inspiration

Functional residual capacity is the volume of gas remaining in the lungs at the resting expiratory level

Lung volumes measured by spirometry do not include the residual volume, which must be determined by a special method.* The residual volume added to the vital capacity gives the total capacity of the lungs. The residual volume constitutes 20 to 25 per cent of the total capacity. As a rule this ratio, RC/TC is increased somewhat with age and in individuals over 60 years it may be as high as 35 per cent.

Vital capacity values obtained by spirometry are evaluated in reference to standards based on criteria of age and physical constitution. Actual vital capacities of healthy individuals may differ as much as 20 per cent from standard averages. The vital capacity found for any subject should not be considered subnormal unless it is more than 20 per cent below that predicted from standard. Vital capacity is lower in the recumbent position. In pulmonary diseases vital capacity can be decreased by every type of affection, namely, congestion, inflammation, fibrosis, bronchial obstruction. It is decreased by conditions interfering with mobility of the chest: pleural effusions, pneumothorax, tight strapping, chest deformity, pain in the chest, rib fracture, abdominal wound, pregnancy, phrenic paralysis, etc. Vital capacity reduction is not pathognomonic of any condition and does not signify pulmonary disease or disability. Conversely pulmonary disability may be present with normal vital capacity.

Residual volume changes may occur in both directions. Decreased residual volume occurs in diffuse pulmonary fibrosis and in diseases of widespread alveolar involvement (granulomatosis). Increased residual volume implies *pulmonary hyperinflation*. This may appear in the form of compensatory hyperinflation following surgical removal of parts of the lungs, or in the form of true emphysema due to structural changes produced by various pulmonary diseases, resulting from bronchial obstruction (asthma), or caused by deformity of the thorax. In the hyperinflated lung the total capacity may remain unchanged and the vital capacity is reduced. This need not affect pulmonary ventilation. In fact the hyperinflated state of the lungs need not of itself imply pulmonary disability, as for example in the case of elderly individuals who are not incapacitated in spite of considerable emphysema.

Total lung capacity is measured by adding the residual volume to the vital capacity. It is decreased in pulmonary affections associated with congestion, edema, fibrosis, or neoplasm, with pleural effusions or pneumothorax, and with pulmonary or pleural conditions that prevent compensatory expansion of parts of the lungs. Total lung capacity is usually normal or only slightly increased in emphysema, but in the presence of partial obstruction of the

* The method now most widely used for determination of residual volume is that by which the N_2 contained in the lungs is washed out by inhalation of pure oxygen for seven minutes. The residual volume is calculated from the amount of N_2 so replaced in the lungs. This method is also useful for determining the efficiency of intrapulmonary mixing of the gases, the so-called "mixing index."

peripheral bronchiolar type, there may be hyperinflation with increased total lung capacity Emphysema with loss of structure results in coalescence of alveoli and the total lung capacity may be reduced although the air spaces appear hyperinflated.

Residual volume to total capacity ratio can be increased either when the residual volume is increased (asthma or emphysema) or when the total lung capacity is decreased (fibrosis). Increased ratio need not imply disabling emphysema In elderly people the residual volume may increase to 50 per cent of total capacity without necessarily causing symptoms.

B *Pulmonary ventilation*

The turnover of gases in the lungs is measured by the rate and depth of breathing. *At rest the average rate is 12 to 14 breaths of 0 5 to 0 6 liters tidal volumes* each, amounting to an average *minute volume of ventilation* of 7 to 8 liters In exercise pulmonary ventilation will increase proportionately with exertion to as much as 12 to 15 times this amount. In utmost exertion *maximal ventilatory capacity* is held to be limited only by the efficiency of the chest bellows as related to the elastic properties of the lungs, which will be considered next under the heading of the mechanics of breathing.

Evaluation of ventilatory function should begin with careful clinical examination which affords much information. We can estimate chest expansion and listen for the quality of breath sounds over various parts of the chest At fluoroscopy we can observe the extent of costal and diaphragmatic excursions Overdistention of the chest, or contraction of parts of it, *hypo- or hyperventilation, can often be recognized* by careful examination However, the latter may also be misleading Patients may seem to overbreathe by appearance of their chest movements but in effect are not turning over adequate volumes of air. We must therefore resort to spirometry since adequacy of ventilation can often be exactly determined only from quantitative measurement When ventilation is subnormal, measurement of minute volume is of great value.

Hypoventilation of milder degrees occurs commonly in various affec*tions of the lungs, bronchi, and pleura* More severe degrees are particularly apt to occur in conditions affecting the respiratory center, such as anesthesia, prolonged anoxia, severe CO_2 retention, or cerebral trauma. It is almost regularly produced by conditions interfering *with mobility* of the chest, such as severe rib fractures

Hyperventilation is primarily a compensatory phenomenon and as such it is seen most regularly in the great variety of pulmonary affections as well as in cardiac states associated with pulmonary congestion The manner in which these *deviations from normal* ventilation affect gas exchange in the lungs will be taken up later

The efficiency of ventilation can be estimated from the amounts of O_2 intake and CO_2 output *as related to the total air turnover.* These measure-

ments can be readily made by means of spirometry. With these data we can calculate the "index of utilization of ventilation" under conditions of rest as well as of exercise

Bronchospirometry enables us to measure the air turnover, the O_2 intake, and the CO_2 output of the two lungs separately This is accomplished by passing a double lumen tube into the airways and connecting the separated outlets from each lung to spirometers It has been found that the right lung is responsible for about 54 per cent of the total ventilation and O_2 consumption

C *Mechanics of breathing* are concerned with the forces involved in the movements of the chest and lungs, the work performed by them, and the evaluation of these forces from the standpoint of clinical function and dysfunction The chest and lungs are held expanded by the tonic contraction of the inspiratory muscles, the periodic increase of which brings about active inspiratory expansion Balanced against this is the force of "elastic recoil" generated in the stretched elastic structures of the expanded lungs and chest This brings about passive expiratory retraction during periods of relaxation of the inspiratory forces Active expiration is brought about by the force of expiratory muscles which become active in effort breathing The work of breathing is performed by these forces overcoming the opposed resistances Analysis of the forces and resistances involved has led to the current concepts of "pulmonary compliance" and of "pulmonary resistance" The former refers to the distensibility of the lungs while the latter refers chiefly to frictional resistance to flow of gases in the airways and to movement of the tissues Pulmonary compliance is measured by change of volume in response to change in pressure Pulmonary resistance is measured by rate of flow *

Economy in work of breathing The mechanical work performed has been calculated from pressure-volume curves obtained during normal breathing at different rates under different conditions and in patients with a variety of pulmonary affections These studies have shown that breathing is so regulated as to make for the greatest possible economy in work expended Under normal conditions slow and deep breathing or rapid and shallow breathing both involve more work than does spontaneous rest breathing at the rate of 15 breaths of 500 cc each per minute Under abnormal conditions on the other hand, the work of breathing is several times (four to five) greater and other patterns of breathing are economical Asthmatics with increased airway resistance tend to breathe more

* A convenient method of measuring pulmonary compliance has recently been elaborated in form of pressure-volume diagrams, intrathoracic pressure changes being recorded from the esophagus Pulmonary resistance is conveniently measured at the same time by spirometers provided with timing apparatus and a fast-moving drum, so that volume and rate of flow per unit of time can be exactly determined

slowly and deeply, while cardiacs with decreased compliance tend to have more shallow and rapid breathing. There is reason to believe that excessive mechanical work performed in breathing plays an important role in dyspnea. More discussion of this will be given later.

Functional tests of mechanical efficiency of breathing include the following two methods which have acquired prominence in modern lung function studies.

(1) *Timed vital capacity* is a test of expiratory flow rate obtained by a forced expiration into a spirometer provided with timing apparatus. A normal individual can expire about 80 per cent of his vital capacity in the first second, more than 90 per cent in two seconds, and close to 100 per cent in three seconds. Pulmonary disease profoundly alters this. In obstructive pulmonary disease (emphysema) we usually find marked slowing of expiratory flow rate The one-second volume of expiration is then reduced *in proportion to severity of the disease, at times even to half of the actual* vital capacity. It should be noted, however, that in pulmonary disease with restricted expansion (reduced vital capacity) but without obstruction, the one-second expiration volume may be normal when referred to actual vital capacity, but greatly reduced when referred to predicted vital capacity.

(2) *Maximal breathing capacity* (M.B C.) is defined as the maximal volume of air that can be breathed per minute Normally this can be produced only by voluntary effort, rarely if ever is it produced by severe exercise In the M B.C test the subject is instructed to breathe into a *spirometer provided with low resistance*, as deeply and as rapidly as he can for 15 seconds, choosing his own rate and tidal volume The frequency should be between 40 and 70 per minute, with tidal volume about half of vital capacity. Normal figures vary in different laboratories as much as 30 per cent, and are much larger for males than for females, and larger for younger than for older age groups of both sexes

Reduction in M B.C must be large to be significant The test is very subjective depending as it does on the subject's desire to co-operate even to the point of exhaustion M B C tests most of the mechanical factors involved in breathing, namely, the available muscular force, the compliance of the lungs and thorax, and airway and tissue resistance Great reduction of M.B C is demonstrable in patients with obstructed airways or with emphysema On the other hand M.B C may be ample in pulmonary fibrosis even when vital capacity is markedly reduced M B C tests afford much information regarding *mechanics of breathing* in many types of cardiopulmonary diseases but a low value is not characteristic of any disease It is an exhausting test and at times might be ill-advised and misleading in weakened patients.

Timed-vital-capacity and maximal-breathing-capacity tests are often performed before and after the administration of bronchodilator *drugs* *This* allows us to determine whether we are dealing with reversible bronchial obstruction, which has an important bearing upon diagnosis and treatment of the condition.

II PULMONARY CIRCULATION

Blood to and from the lungs is driven by the pumping action of the heart, but its transmission through the vast pulmonary capillary bed depends upon obscure factors which regulate the flow of blood within the alveoli in close correlation with alveolar ventilation The role of the heart is attested by the consequences of obstruction in the pulmonary circulation upon the right side of the heart (*cor pulmonale*) The role of correlation of ventilation and blood flow at the alveolar level is attested by the pulmonary hypertension resulting from anoxia and carbon dioxide retention The pressure levels in the pulmonary circulation are mere fractions of those which prevail in the systemic circulation Furthermore these low pressure levels are not affected either by doubling of cardiac output or by loss of half of the vascular bed (pneumonectomy) All of this clearly points to the prodigious capacity of the pulmonary vascular bed either in the form of reserve channels, or in the great distensibility of available channels, and probably in both

The pressure in the pulmonary vascular bed begins to rise only when cardiac output has increased more than threefold, as in exercise It rises sharply on exercise when the vascular bed has been reduced to less than its normal half (as in patients with one lung on exercise) The pulmonary vascular bed usually becomes reduced with advancing age Pulmonary diseases obliterating or compressing parts of the vascular bed have the same effect This is particularly true of disorders of the pulmonary circulation (sclerosis, thrombosis, embolism, etc)

A considerable amount of information about the level of pressure in the pulmonary vascular bed may be gained from fluoroscopic examination of the chest with special attention to the pulmonary artery and the right ventricle For complete evaluation of the pulmonary circulation it is necessary to include cardiac catheterization

III GAS EXCHANGE

Two sets of phenomena are involved in gas exchange adaptation of functions at the alveolar level, and the physicochemical criteria of the transfer of the gases between blood and air

A *Adaptation of functions at the alveolar level* is perhaps the most crucial part of pulmonary function Its importance will be readily appreciated if we consider that the ultimate purpose of lung function is gas exchange, that the rate of the latter is dictated by momentary requirements of metabolism in the body, and that this fluctuates between the extremes of the low basal level at rest and a tenfold increased level in severe exercise Normal lungs are prodigiously endowed with facilities for a very wide range of variations in function (It has been estimated that there are 750 millions of alveoli with a diffusing surface of about 100 square meters)

Under pathologic conditions also, these facilities afford ample reserves for compensatory function Considering the vast number of alveoli, the size of the pulmonary vascular bed, and the extent of the diffusing surface,

it is easy to see how exigencies of greatly increased function in utmost exertion are met by normal lungs The difficult problem seems to be rather that of how normal lung function of basal level at rest is essayed and how it is constantly adapted to such a wide range of fluctuations in momentary requirements of gas exchange. Obviously this involves exquisite adaptation of ventilation, blood flow, and diffusing surface at the alveolar level.

The exact nature of the mechanism by which this exquisite adaptation of function at the alveolar level is accomplished remains to be elucidated Much recent evidence points to the fact that this mechanism is keyed to the tension levels of O_2 and CO_2 in the blood and in the gases in the alveoli. It is fairly well established that the tension levels of these gases in the blood have a direct local influence on capillary blood flow and on pressure levels prevailing in the pulmonary vascular bed, as well as on alveolar ventilation In normal lungs this mechanism plays a role in directing blood flow to ventilated alveoli and diverting ventilation from inactive non-perfused alveoli There is much evidence to indicate that even under certain abnormal conditions this mechanism acts to divert the flow of blood from nonfunctioning to normally functioning parts of the lungs.

Ventilation of alveoli without correlated adequate blood flow will result in "deadspace ventilation effect" Blood flow in alveoli without correlated adequate ventilation will manifest itself in "venous admixture effect." Abnormalities of diffusion surface adaptation will result in decreasing diffusing capacity The implications of these upon gas exchange will be discussed under the next heading

B *The physicochemical criteria* of transfer of the gases are different for each of them

Oxygen uptake is determined by the chemical combination that this gas enters into with hemoglobin This association enables blood to become fully saturated with O_2 (97 per cent of capacity), even at levels of O_2 *tension far below that prevailing normally in the lungs during* ventilation at rest Not only is the blood passing through the normal lung saturated with O_2 to its full capacity with minimal breathing under conditions of rest, but even with subnormal ventilation, O_2 saturation of the blood will not suffer until O_2 tension falls below *75 mm Hg In the normal lung* O_2 saturation of the blood cannot be significantly raised by increasing the tension of O_2 through hyperventilation or inhalation of O_2 Under abnormal conditions, however, hyperventilation and O_2 inhalation, and especially the latter, readily relieve unsaturation (anoxia). Subnormal saturation of arterial blood may be detectable by cyanosis, bluish discoloration of the mucosal surfaces and, if of sufficient degree, discoloration of skin. However, *cyanosis is not a reliable* indicator of arterial anoxia as it may result from local slowing of capillary circulation and at times may not appear until anoxia is very severe Oxygen unsaturation is usually measured by exact gas analytical methods. Recently spectrophotometric methods of

oximetry have been elaborated for determination of arterial O_2 saturation levels These are now widely used, especially where continuous recording is desirable, as during anesthesia.

Carbon dioxide elimination The CO_2 content of venous blood is in direct proportion to the pressure level of this gas in this blood In passing through normal lungs this pressure (pCO_2) is reduced from the venous level of the 46 mm Hg to the arterial level of 40 mm Hg Because CO_2 has a much greater diffusibility (20 times greater) than O_2 and because the CO_2 content of the blood and the alveoli depend more directly upon the pressure level of this gas, carbon dioxide elimination is far more immediately affected by breathing, *i e*, pulmonary ventilation Hyperventilation results in the blowing off of excess amounts of CO_2, while it has no effect on O_2 uptake in the normal and little effect in the abnormal lung Hypoventilation, on the other hand, will immediately affect CO_2 elimination and will result in CO_2 retention of proportionate degree, first in the lungs and then in the blood If severe, hypoventilation will soon result in O_2 want also.

By virtue of CO_2 elimination, lung function plays the most important role in the regulation of the acid-base balance of the body under homeostatic control from the respiratory center. The phenomena which result from this will be discussed below in connection with regulation of pulmonary function

Gas exchange disturbances and their evaluation

Anoxia is by far the more common manifestation of gas exchange disturbance Indeed anoxia is often present when CO_2 is being eliminated in excess because of hyperventilation due to the anoxia or the pulmonary disease itself In contrast *CO_2 retention* does not usually occur without simultaneous presence of anoxia, except in patients under O_2 inhalation or during anesthesia By means of gas analytical studies it has become possible to differentiate between the following four types of gas exchange disturbances

Hypoventilation refers to pulmonary ventilation inadequate in proportion to gas exchange requirements It is usually associated with decrease in tidal volume or rate of breathing or with increase in deadspace (e g, air-space abnormalities in the lungs) It always results in CO_2 retention Hypoventilation is particularly apt to escape attention during surgical anesthesias when high concentrations of O_2 are used which prevents anoxia, but cannot prevent CO_2 retention

Venous admixture (venous to arterial shunts in the lungs) is present when many alveoli or large segments of the lungs are blocked to pulmonary ventilation but not to the circulation, so that unarterialized blood is passing through the lungs This is the only condition in which the anoxia produced cannot be corrected by inhalation of O_2 in high concentration Exercise aggravates this anoxia as blood becomes more venous CO_2 retention is slight since the lungs can hyperventilate and blow off more CO_2 in the compensating areas

Impaired diffusion as an isolated phenomenon is chiefly characteristic of a group of specific diseases involving the alveolar structures (granulomatosis, sarcoidosis) It leads to marked anoxia that is exaggerated by increased CO_2 elimination, as patients with these diseases tend to hyperventilate. *Diffusing capacity may become so low that these patients can be kept alive* only by inhalation of O_2 in high concentration, which can compensate for the defect. In patients kept alive in this manner, CO_2 retention may occasionally result.

Dysfunction at the alveolar level is variously described as failure of mixing or distribution, or as uneven ventilation-blood flow relationship. This is characterized by anoxia which is completely compensable by O_2 inhalation, *but often at the cost of hypoventilation leading to CO_2 retention* As the anoxic stimulus to breathing is removed by inhalation of O_2, these patients tend to lapse into a state of hypoventilation with CO_2 retention

Combinations of the above four types of gas-exchange disturbances occur frequently in the same patients In emphysema there may be hyperventilation, abnormal ventilation/blood flow ratio, and impaired diffusion The same may be said of some patients with open hemithorax.

Even serious pulmonary disease need not lead to anoxemia. This is a clinical fact that will bear repeated emphasis. In some cases lung areas affected by carcinoma, cysts, or tuberculous lesions receive little blood, but as long as the rest of the lungs function adequately, O_2 saturation remains normal *The same applies after pneumonectomy if the remaining lung is* normal.

The presence of anoxemia does not necessarily imply symptoms or disability. Arterial O_2 unsaturation of moderately low degree (between 90 and 85 per cent) does not usually disable patients. Even lower degrees (80 per cent and below this level) of O_2 saturation are compatible with active life, particularly in patients with congenital heart or anatomic shunts *These patients usually have polycythemia, which greatly increases their O_2* holding capacity Up to a certain point this is a great factor of compensation but it is limited by the excessive increase in blood viscosity which eventually increases the burden upon the heart or may result in thrombosis

In contrast, severe symptoms and disability are produced in pulmonary diseases by the increased breathing effort of maintaining alveolar gas exchange and normal O_2 saturation In asthma and emphysema severe dyspnea and disability may be present in spite of normal O_2 saturation and normal CO_2 level, they are probably related to mechanical factors in ventilation and the increased work of breathing

IV. Regulation of Lung Function

It is a part of the homeostatic mechanism of the body to control lung function constantly in accordance with momentary metabolic requirements This regulatory mechanism is exceedingly complex and far from comprehended We know that it originates with countless stimuli streaming from all parts of the body in the form of proprioceptive reflexes The stimuli

passing along the vagal pathways to the respiratory center in the medulla are of paramount importance Special chemo, pressor and thermal receptors placed along the peripheral vagal pathways (aortic, carotid bodies, etc) act as stations for feedback mechanisms

According to recent concepts of multiple factor control of breathing, numerous stimuli are active in its regulation, in such a manner that their summation effect determines the actual extent of ventilation Included among these stimuli are three chemical agents (H-ion concentration and tension levels of CO_2 and O_2 in the blood) which also act as feedback control mechanisms, since every change in ventilation in turn affects the blood levels of these chemical agents The acid-base balance of the body is based on this regulatory mechanism as follows

The normal chemical reaction (pH) of the blood is maintained by a buffer system based on the ratio of $BHCO_3$ to H_2CO_3 rather than upon the actual contents of base and acid Normally this ratio is maintained by pulmonary ventilation which keeps the level of CO_2 in arterial blood (pCO_2) at about 40 mm Hg When pCO_2 rises above this level, alveolar ventilation increases by stimulation from the respiratory centers (medulla). This delicate control mechanism is dependent upon normal sensitivity of the center, upon intact nervous connections between the respiratory center and the chest, and upon normal conditions in the lungs Hypoventilation may occur because of a defect in any one of these factors in breathing This will result in accumulation of CO_2 When arterial pCO_2 rises, an increase in carbonic acid (respiratory acidosis) will call forth a corresponding increase in buffer base (chiefly by renal compensation) to keep the acid-base balance normal Under these circumstances the total plasma CO_2 may or may not be increased In the interpretation of this, much confusion prevails because it is not generally appreciated that total blood CO_2 may be either high or low in either acidosis or alkalosis It is important to emphasize that total blood CO_2 will be high in respiratory acidosis and metabolic alkalosis, and it will be low in respiratory alkalosis (hyperventilation) and metabolic acidosis (e g, diabetes) Data on total blood CO_2 content should always be interpreted on the basis of the blood pH and of plasma pCO_2 Respiratory acidosis is present only when pCO_2 is high and pH is low. If pH is high and pCO_2 is low, respiratory alkalosis is present On the other hand blood CO_2 data can be readily interpreted in the light of knowledge of the pulmonary status of the patient in question

The influence of psychic stimuli upon breathing is too well known to need further discussion, but it should be pointed out here that this influence brings regulation of lung function into that twilight zone between psychic and somatic processes in which it is no longer possible to separate subjective from objective phenomena This is particularly apparent in the great individual differences in the threshold of dyspnea. In the clinical analysis of dyspnea it is therefore often impossible to assess the proportion of objective and subjective factors.

From the clinical standpoint, the striking individual differences in th

sensitivity of the respiratory center are of great importance We are ignorant of the reasons for these differences. The facts are that some patients with pulmonary insufficiency retain high sensitivity of the respiratory center, driving the breathing mechanism to continued effort which, in spite of dyspnea, keeps gas exchange up to normal levels, while other patients show a striking lack of response in spite of deep cyanosis due to severe anoxemia In this so-called non-dyspneic form of pulmonary insufficiency, chronic anoxia eventually leads to heart failure. This type of pulmonary insufficiency can at least temporarily be combated by mechanical respirators, of which there is now a variety in clinical use.

PULMONARY DYSFUNCTION AND ITS ASSESSMENT IN LUNG CANCER

The effect of a pulmonary cancer on lung function can vary tremendously. In many instances, particularly in cases with a small peripheral carcinoma, no demonstrable abnormality in pulmonary function can be demonstrated by the technics available at present. Since there is a rather wide variation in what is considered to be within the normal range, small variations in function cannot be considered as abnormal This does not necessarily imply that the pulmonary function of most patients with a small peripheral carcinoma is normal. Because of the high incidence of bronchial irritation from smoking, chronic bronchitis, and especially pulmonary emphysema among individuals with lung cancer, the pulmonary function often shows varying degrees of impairment due to these chronic changes Thus in many patients such disturbances in pulmonary function as are present may be largely due to alterations in function that antedated the development of the neoplasm. This is particularly true in the elderly patient.

In any consideration of the decrease in pulmonary function that might result from a bronchogenic carcinoma the location of the neoplasm in relation to the tracheobronchial tree will be of considerable importance. A tumor in a main bronchus which seriously interferes with the ventilation of an entire lung will tend to cause greater impairment of ventilation than a neoplasm limited to a lobar or segmental bronchus When the growth does not narrow the bronchial lumen sufficiently to interfere with ventilatory exchange, little functional impairment may occur unless distal pneumonitis is present.

The effect of bronchial obstruction on pulmonary function is considerably influenced by the rapidity with which the process occurs. When one segmental bronchus of a lobe becomes gradually occluded by a tumor, the changes in lung volumes and capacities may be slight because of the compensatory hyperinflation of the adjacent uninvolved segments.

Even obstruction to the bronchus of an entire lobe may be associated with only minor reductions in lung capacities provided the changes occur gradually and are not accompanied by extensive pneumonitis or significant pleural reaction Moreover, the ability of the remainder of the lung to undergo compensatory hyperinflation without resulting in gas exchange disturbances will influence the extent of functional impairment. When diffuse pulmonary emphysema is present, the hyperinflation of the adjacent lobe may lead to dysfunction at the alveolar level and be manifest by considerable increases in the residual volume and reduced efficiency of ventilation In patients with severe emphysema, anoxemia may occur

Since maximal pulmonary ventilation is dependent on the efficiency of the chest bellows, any chest pain, impaired respiratory motion, or pleural complications may profoundly reduce lung function even in the absence of extensive parenchymal lung disease This is dramatically demonstrated by the dyspnea and cyanosis which an acute pleuritis can produce. In some cases the roentgen evidence of pleurisy may be indeed meager Fluoroscopy will demonstrate better the impairment of ventilatory motion Marked reduction in maximum breathing capacity may occur from splinting of the chest wall due to pain or thickened pleura Pleural effusions can obviously decrease lung volumes and capacities.

There is a tremendous difference in the degree of disturbance of lung function caused by an acute lobar pneumonia as compared to chronic pneumonitis of a lobe secondary to slow bronchial occlusion In the later instance the gradual reduction in pulmonary circulation through the involved lobe as atelectasis occurs obviates significant venous admixture and thus anoxemia and carbon dioxide retention rarely occur in the absence of pulmonary emphysema Even when a tumor has obstructed the main bronchus to an entire lung, the blood gases are usually normal Therefore whenever anoxemia is demonstrated, significant emphysema of the opposite lung must be suspected provided acute pneumonitis or pleuritis is not a factor If the patient has severe bronchospasm or asthma, anoxemia may be only intermittently present and may be corrected by bronchodilators

Considering the great multiplicity of changes produced by cancer in the lung and its complications, it is not surprising that so many types of pulmonary dysfunction may ensue

Ventilatory impairment predominates when tumors cause 1) interference with flow of air by obstructing or compressing bronchi; 2) interference with mobility of the lung by pleural effusions, or large tumor masses, and 3) interference with mobility of the diaphragm by involvement of phrenic nerve

Pulmonary insufficiency may be produced when the area of functioning lung parenchyma is drastically reduced by: 1) tumor blocking out a whole lung (obstruction of main bronchi or vessels), 2) widespread tumor interfering with gas diffusion across the alveolar surface (alveolar carcinomatosis), and 3) overdistention of an emphysematous remaining lung following pneumonectomy.

Ventilatory impairment and pulmonary insufficiency are frequently concomitant. The functional implications of these have been discussed in the preceding part of this chapter. Dyspnea is the most conspicuous clinical manifestation of pulmonary dysfunction in lung cancer as it is in pulmonary diseases in general The question naturally arises as to how much reliance can be placed on dyspnea as an index of pulmonary dysfunction. The causes and features of dyspnea in cancer of the lung therefore merit special discussion.

Dyspnea as an Index of Pulmonary Dysfunction in Cancer of the Lung

The interpretation of dyspnea may vary with the stage of the neoplastic process. Occasionally a patient with limited pulmonary involvement may complain of dyspnea Often such shortness of breath is experienced only intermittently and may be a subjective sensation not confirmed by objective observation. As the evident pulmonary changes do not account adequately for such dyspnea, we must assume that reflex disturbances of breathing are responsible Transient recurrent episodes of dyspnea may result from secretions eliciting bronchospastic reactions in already irritated bronchi. Dyspnea early in the disease is no doubt an expression of some disturbance in lung function but it certainly is not an index of pulmonary insufficiency Particularly from the standpoint of treatment, it must not be interpreted as a contraindication to resection which might be expected to relieve this type of dyspnea. Hence it is important to understand that in cancer of the lung there are many instances in which a history of intermittent dyspnea does not contraindicate resection.

Dyspnea in advanced lung cancer is readily explained by the pulmonary dysfunction produced by the disease Such correlation might suggest that dyspnea is a reliable index of pulmonary dysfunction Yet many patients, even with extensive pulmonary neoplasms, appear to suffer relatively little from dyspnea Slow growth permits gradual adaptation to the diminished function. Moreover, the great reserve capacity of the lungs enables most patients to tolerate marked losses in functioning lung parenchyma. Another important factor is the great individual differences in "dyspnea threshold" Individual differences in sensitivity of the respir-

atory center account for dyspneic and non-dyspneic forms of pulmonary insufficiency Thus dyspnea cannot be relied upon as an index of pulmonary dysfunction for practical clinical purposes. In some cases we might tend to refrain from a resection which is feasible while in other cases we run the risk of pulmonary failure as a result of resection. Lung function studies may clarify this situation

ASSESSMENT OF PULMONARY FUNCTION

Since pulmonary resection is the treatment of choice for operable cases, the patient's tolerance to the intervention must be estimated So far relatively little use has been made of the functional tests considering the large number of cases operated upon for lung cancer. Several reasons for this may be mentioned As yet no simple tests are available for a reliable estimation of the entire functional status of the lung A battery of tests is required for complete evaluation, and special facilities are required for the more complicated tests The chief reason, however, militating against the wider use of functional studies in cancer patients, is the fact that life is at stake and considerable risk of pulmonary insufficiency seems justified.

The usual practice is to rely on a broad clinical survey of the general functional status of the patient He is considered fit for operation if there is no history of previous pulmonary disease and if the pulmonary involvement is restricted to one lung When emphysema is suspected, due consideration must be given to the effects of pulmonary resection on a patient's cardiorespiratory function in the postoperative period and in later years, if unnecessary morbidity and mortality are to be avoided The incidence of emphysema is high in the age group with lung cancer Because some emphysematous patients tolerate pulmonary resection fairly well whereas others do poorly, it behooves the surgeon to attempt to make an individual assessment in each case The presence of obvious pulmonary hypertension should be a warning to the surgeon that any extensive pulmonary resection may be disastrous When the pulmonary artery is found to be considerably enlarged and less compressible than normal at operation, a clinical diagnosis of pulmonary hypertension is warranted. In this situation the greatest conservation of pulmonary tissue and thus the least additional reduction in the pulmonary vascular bed is indicated In such cases the difference in morbidity and mortality of lobectomy and pneumonectomy may be considerable

Functional studies in a large number of cases before and after major thoracic surgery have been reported in the literature. For the most part these were made on patients with tuberculosis and a variety of other pulmonary diseases including a small proportion with lung cancer From this clinical experience which is quite applicable to most contingencies

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Dyspnea as an Index of Pulmonary Dysfunction in Cancer of the Lung

The interpretation of dyspnea may vary with the stage of the neoplastic process. Occasionally a patient with limited pulmonary involvement may complain of dyspnea. Often such shortness of breath is experienced only intermittently and may be a subjective sensation not confirmed by objective observation. As the evident pulmonary changes do not account adequately for such dyspnea, we must assume that reflex disturbances of breathing are responsible. Transient recurrent episodes of dyspnea may result from secretions eliciting bronchospastic reactions in already irritated bronchi. Dyspnea early in the disease is no doubt an expression of some disturbance in lung function but it certainly is not an index of pulmonary insufficiency. Particularly from the standpoint of treatment, it must not be interpreted as a *contraindication to resection* which might be expected to relieve this type of dyspnea. Hence it is important to understand that in cancer of the lung there are many *instances in which a history of intermittent dyspnea does not contraindicate resection.*

Dyspnea in advanced lung cancer is readily explained by the pulmonary dysfunction produced by the disease. Such correlation might suggest that dyspnea is a reliable index of pulmonary dysfunction. Yet many patients, even with extensive pulmonary neoplasms, appear to suffer relatively little from dyspnea. Slow growth permits gradual adaptation to the diminished function. Moreover, the great reserve *capacity* of the lungs enables most patients to tolerate marked losses in functioning lung parenchyma. Another important factor is the great individual differences in "*dyspnea threshold.*" *Individual differences* in sensitivity of the respir-

EFFECT OF PNEUMONECTOMY UPON THE FUNCTION OF THE REMAINING LUNG

Since pneumonectomy is required in most cases of primary cancer of the lung, the effect of removal of one lung is a question of considerable importance in these patients Although many studies of pulmonary function after pneumonectomy have been done, final evaluations must await more complete studies carried out over several decades. Our present information strongly suggests that one of the most important factors in determining the pulmonary function years after lung resection is the status of the uninvolved lung at the time of pneumonectomy (Fig 121A and B) Although the mediastinal displacement that occurs in the weeks and months after pneumonectomy is recognized to have a detrimental effect on pulmonary function in some individuals, the degree of mediastinal shift is not the prime factor affecting the respiratory function Comparable degrees of mediastinal deviation have varying effects in different patients depending particularly on the normalcy of the remaining lung. The hyperinflation of the contralateral lung after pneumonectomy may cause no certain emphysema of that lung if it was free of emphysema prior to operation In contrast, the overinflation of an already emphysematous lung can lead to respiratory insufficiency. Thus the most important single factor in determining the influence of pneumonectomy on respiratory function is the functional integrity of the remaining pulmonary tissue The physiologic as well as the anatomic adjustment after pneumonectomy is better after left-sided pneumonectomy than when the right lung is removed The right lung of humans constitutes about 54 per cent of the total pulmonary tissue whereas the left lung comprises 46 per cent Although this difference seems small, it may still be significant, especially if pulmonary fibrosis with associated reduction in the pulmonary vascular bed is already present What effect the displacement or rotation of the cardiovascular structures of the mediastinum after pneumonectomy may have on cardiorespiratory function awaits further elucidation

Although many patients who have undergone pneumonectomy for cancer and other conditions have had respiratory functional studies, in only a relatively small number are accurate data concerning the preoperative status of the remaining lung available Without such data as a base line, it is difficult to segregate the effect of mediastinal displacement per se on a normal lung as compared with an already emphysematous one Moreover, the detrimental effect of hyperinflation of a lung might require many years for its obvious development Thus continued long-term

arising in lung cancer cases, the following data of interest can be gleaned. The most common cause of pulmonary insufficiency is obstructive emphysema. The functional tests of greatest value are, therefore, those which are particularly sensitive indicators of this condition. This refers primarily to the estimation of maximal breathing capacity (M.B.C.). This test needs to be supplemented at times by determinations of the intrapulmonary mixing index with estimation of residual volume. Maximal breathing capacity (M.B.C.) is generally acknowledged to be the most useful single functional test. It affords an adequate measure of breathing efficiency not only in its mechanical aspects but also as regards time and quantity factors of ventilation. It has been generally found to show a high degree of correlation with gas exchange except in the few conditions in which interference with gas diffusion predominates, such as diffuse carcinomatosis. The latter can be clearly discerned from clinical and roentgen features. Experience indicates that when M.B.C. is reduced to less than half the predicted normal, pulmonary function may be inadequate for pneumonectomy unless extreme care is given to pulmonary ventilation during operation. Gaensler found that lesser impairment of vital capacity than of maximal breathing capacity was indicative of obstructive ventilatory difficulty. Birath found the residual volume fairly constantly increased in dyspneic patients and the ratio of residual to other lung volumes significant. Gaensler used residual volume and intrapulmonary mixing index determinations in combination with maximal breathing capacity to distinguish simple hyperinflation from true emphysema.

Recently efforts have been made to determine the reserve capacity of the remaining lung by producing "physiologic pneumonectomy." This refers to the combination of tracheal and cardiac catheterization with balloon blocking of the main bronchus, as well as the pulmonary artery of the lung to be resected. If the remaining lung can accommodate the doubling of blood flow without any or with only minimal rise of pressure and without the development of hypoxia, the prognosis is regarded as favorable. Current experience suggests that doubling of pulmonary artery pressure under these conditions may be a warning of postoperative pulmonary failure with subacute *cor pulmonale*. The test of combined cardiac catheterization with bronchospirometry is still a formidable procedure not likely to be practiced soon on a wide scale. Bronchospirometry itself is a special test made use of fairly frequently. It is most helpful when information is sought about the separate functions of each lung. The O_2 uptake is often a valuable guide in the prognosis regarding the remaining lung.

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12

Surgical Treatment

HERBERT C. MAIER

INTRODUCTION AND HISTORICAL BACKGROUND

The fundamental concept underlying surgical treatment of cancer of the lung is the *excision of all neoplastic tissue. It follows therefore that* the clinical efficacy of such therapy depends largely on the time at which the operation is performed in relation to the biologic life history of the neoplasm. Although the extent of the surgical procedure may influence the clinical result, it should be appreciated that the malignant potentialities of the cancer play the predominant role.

Historically the earliest efforts at surgical therapy in cancer of the lung consisted of attempted destruction of the tumor in the lung by cauterization through a thoracotomy wound. Then as the techniques of lobectomy were gradually developed, resection of a lobe of the lung with neoplasm was attempted with increasing frequency. It is said that prior to 1933 there were only six recorded cases of successful lobectomy for carcinoma of the lung with survival for a year following operation. Efforts to destroy centrally located bronchogenic carcinoma by cauterization or piecemeal removal through the bronchoscope were also made. These endoscopic treatments were successful only in a palliative way unless the neoplasm was one of the rarer tumors of low-grade malignancy such as the bronchial adenoma. In 1933 Graham reported the first successful pneumonectomy for lung cancer (12). Since then there has been a rapid development in the application of surgical therapy to neoplasms of the lung and a great reduction in the operative risk. Advances in anesthesiology, blood replacement, antibiotics, and improved surgical techniques and physiologic management have contributed mightily to the reduction in surgical morbidity and mortality in the past two decades. Today the chief obstacle to successful surgical therapy is the unfavorable biologic characteristics of many pulmonary neoplasms.

The most fundamental weakness in our present-day estimate of the potential efficacy of surgical treatment in cancer is due to our lack of information concerning the degree of relationship between the size and

age of the primary neoplasm and the possibilities or probabilities that metastatic foci are already developing. The mode, time, and distribution of earliest metastatic spread of each type of cancer of the lung are obviously important factors in determining the potential value of more radical operations which remove larger areas of lung tissue, bronchi, hilar and mediastinal lymphatics, and contiguous structures. Lacking this fundamental information concerning the biological time schedule of the spread of cancers of the lung, the efficacy of surgical therapy has to be analyzed on the basis of the results obtained by various types of surgical treatment performed in the clinically recognizable phases of the neoplasm. Moreover the response to treatment of each of the different pathologic types of cancer of the lung must be individually assessed before an accurate evaluation can be expected.

Present-day cancer surgery is based on the concept of radical removal of the diseased area with the adjacent lymphatics. In most cases of bronchogenic carcinoma this requires a total pneumonectomy. When the neoplasm is located well away from the hilus of the lung, lobectomy may be considered satisfactory. The extent of hilar and mediastinal lymph node dissection practiced by various surgeons varies considerably. The pros and cons of the more radical procedures will be discussed in a later section in this chapter.

INDICATIONS AND CONTRAINDICATIONS FOR SURGICAL TREATMENT

At present the primary indication for surgical treatment in cancer of the lung is the known or suspected presence of the neoplasm without the known existence of extrathoracic metastases or extensive mediastinal invasion. The surgical literature on cancer frequently classifies cases in "operable" and "inoperable" groups. Since different authors use these terms in different ways, confusing and contradictory statements are frequently found and a superficial analysis of reports may lead to erroneous conclusions. Some surgeons list those cases as "operable" in which a portion or the whole lung may have been removed regardless of whether gross tumor tissue was left behind. To other surgeons a lesion would seem to be "inoperable" if any cancer tissue was known to have remained. In some reports the cases are divided into three categories: 1) an "inoperable" group in which the pulmonary neoplasm was not considered removable, 2) an "operable" group in which the surgical procedure was considered to be only palliative in that it was considered likely that some neoplastic tissue was or may have been left behind (these may be called "palliative operations"), and 3) an "operable" group in which all gross tumor tissue was removed and where there was some reasonable expe

tion that the neoplasm had been surgically eradicated (sometimes called "operations for cure").

Since many a case of cancer of the lung is in an advanced stage when the surgical treatment is undertaken, the possible advantages of extending the surgical attack have rightly engaged the attention of many surgeons As an offshoot of this trend there has been an increasing tendency to label operations which are admittedly incomplete from the standpoint of total excision of neoplastic tissue as "palliative" operations. This is a subject of considerable debate and will be discussed in a separate section later in this chapter. At this point consideration will be given to the efficacy of surgical intervention in the hope of curing cancer of the lung

Thoughts and analyses concerning surgical treatment become utterly confused unless the present-day knowledge of the life history of the neoplasm is employed as a background in evaluating the surgical results. Although it is appreciated that certain less common tumors of the bronchi and lung that are classified among the cancers of the lung have a far better prognosis, treated or untreated, than the vast majority of bronchogenic cancers, the fallacy of considering all squamous and adenocarcinomas as a single disease is obvious from a careful analysis of clinical experience. Although there are admittedly real pitfalls in extensive subclassification of cancers of the lung, yet we must hope that in the future a better understanding of their life history will place surgical treatment for a particular patient on a less arbitrary basis. It is most important that the pathologic data be closely correlated with the clinical behavior and response to surgery so that the over-all picture may be clarified. The considerations concerning surgical treatment in the common forms of epidermoid and adenocarcinoma which constitute the vast majority of the bronchogenic cancers encountered will first be discussed. Later the modification in surgical approach dictated by special less common forms of cancer of the lung will be considered

A discussion of the surgical treatment of cancers of the lung would be incomplete if the important role of exploratory thoracotomy in the management of undiagnosed circumscribed solitary pulmonary lesions was not emphasized. Since the proper therapy for the majority of isolated pulmonary masses is surgical excision, the thoracotomy is performed with the idea of excising the lesion irrespective of its pathologic nature except in rare instances. The extent of the pulmonary resection would be determined by the pathologic findings at operation. It is best to explain to the patient that the reason operation is recommended is because a roentgenologically detected solitary lesion which is not a transient infiltrate had best be removed almost regardless of its nature, and that preoperatively one often cannot definitely ascertain whether it is benign or malignant. Since many persons who have a small asymptomatic pulmonary lesion

may tend to procrastinate, the great difference in the later survival rate after surgical therapy between asymptomatic and symptomatic cancers must be emphasized Patients who feel entirely well often do not readily agree to an "exploratory operation to see what the trouble is" because they may look upon the operation as an evil necessitated by the physician's inability to make a diagnosis The patient then feels that he has to be "opened up" merely for diagnostic reasons It is far better psychologically to present the problem in such a way that he looks upon the operation as a therapeutic rather than a diagnostic one since it is really both, combined into one

In this discussion a cancer of the lung is defined as inoperable if removal of all gross tumor tissue is not possible These cases are subdivided into those in which there is evidence of extrathoracic metastases and are thus considered inoperable without a thoracic exploration, and the second group in which inoperability was determined at the time of exploratory thoracotomy The findings indicating inoperability without exploratory thoracotomy will be discussed first Evidence of such inoperability may be considered in two categories 1) absolute evidence of distant metastases as indicated by pathologic confirmation of such metastases, and 2) indirect or presumptive evidence of extrathoracic metastases In this latter category the history, physical findings, and laboratory evidence may all contribute

Determination of the Presence of Extrathoracic Metastases

In the patient with suspected or known bronchogenic carcinoma careful examination should be directed especially to those areas in which metastases frequently occur Careful palpation of the cervical region for possible lymph node involvement is important An effective way of carrying out this examination is to have the examiner stand behind the patient so that the tips of the examiner's fingers can more readily explore the lower anterior cervical area behind the upper portion of the clavicles where involved nodes are most frequently found By this examining position the simultaneous bilateral examination of the neck may be made with the examiner's two hands so that he can better interpret a difference on the two sides and thus more readily differentiate between normal anatomical landmarks and small lymph node enlargements. It should be appreciated that a firm node, though small, is more likely to be significant than a larger, softer node Moreover an enlarged node just back of the clavicle is more likely to be significant than a similar node in the group that drains the tonsillar area, or in the posterior cervical chain

Whenever a suspicious cervical lymph node is palpated, a biopsy is indicated If a metastasis is proven, thoracotomy for the lung lesion is not indicated If there is diffuse swelling of the neck as seen with vena

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however that negative roentgen findings do not rule out osseous or adjacent soft tissue metastases. It is not unusual to have a history of localized pain present for months before roentgenologic confirmation of the bony lesion is established. Naturally if the metastatic involvement is limited to the soft tissues, radiologic examination may be of little aid. The vertebral bodies and ribs are the more frequent sites of osseous metastases. A blood alkaline phosphatase determination may be of value. A complete roentgenologic investigation of the bony skeleton only rarely will detect unsuspected bone metastases from a bronchogenic cancer when the patient is free of discomfort on careful questioning. Confusion should not arise between bone metastases and bone tenderness and arthritis due to pulmonary osteo-arthropathy. The latter is due to some metabolic or circulatory influence of the pulmonary neoplasm and is not indicative of metastatic disease.

If the patient manifests marked loss of weight and appears cachectic, the possibility of an operable lesion is remote unless secondary suppuration distal to a bronchogenic carcinoma can account for the physical deterioration. Although pulmonary infection is a frequent accompaniment of bronchogenic carcinoma, the patient rarely presents a septic appearance. On the contrary, it is not rare to find that the patient has a fever, sometimes even of some magnitude, without his being aware of it. Occasionally the patient with bronchogenic carcinoma and secondary suppuration gives a history of weight loss which was then followed by a gain in weight as the inflammatory component responded to antibiotic therapy.

If the patient complains of marked weakness and the blood pressure is found to be below 100 mm Hg systolic, adrenal metastases may be suspected. Although adrenal metastases from bronchogenic carcinoma are common, clinical manifestations of such involvement is usually lacking due to the fact that sufficient uninvolved adrenal tissue remains. Lumbar pain not explained on the basis of osseous metastases may be present in the patient with adrenal metastases.

In the absence of histologic proof of extrathoracic metastatic disease it is wisest not to rely completely on any one finding as definite evidence that the cancer of the lung has metastasized. All of the factors and their probable significance should be given due consideration. For instance, the probability of hepatic metastases would be much greater in a patient with liver enlargement who also had marked weight loss, as compared with another patient in whom physical examination revealed a similar moderate degree of diffuse hepatic enlargement without weight change.

In summary, exploratory thoracotomy for proven cancer of the lung is not indicated when there is pathologic confirmation of metastases in extrathoracic lymph nodes or when skin nodules of recent appearance

caval obstruction due to mediastinal extension of a bronchogenic carcinoma, the cervical lymph nodes may be enlarged without being firm. Such enlargement may be due to the lymphatic obstruction from the mediastinal disease rather than due to metastases in the cervical lymph nodes. Therefore soft enlarged cervical lymph nodes in the presence of venous and lymphatic obstruction do not necessarily indicate cervical neoplastic involvement. This point is of some practical importance because a cervical lymph node biopsy in the presence of marked lymph edema and congestion of the neck is a rather unsatisfactory procedure unless a truly firm lymph node is the goal of the exploration Metastases to axillary lymph nodes from a bronchogenic carcinoma are rare compared to the incidence of mediastinal and cervical involvement. Since enlarged soft lymph nodes are a frequent finding in the axillae of males, particularly in those who have done manual labor, biopsy of an axillary lymph node is usually not rewarding unless the lymph node is of definitely firm consistency

The liver should be carefully examined for evidence of enlargement or nodularity. Bronchogenic carcinoma frequently metastasizes to the liver and in some instances these metastases are so extensive and rapid in their growth as to lead to massive hepatic enlargement. It is often difficult to palpate definite nodules within the liver when hepatic metastases from the lung are present, but the size of the liver itself, and particularly a rapid change in size, may give a clue to the diagnosis.

Since bronchogenic carcinoma frequently metastasizes to the central nervous system, particularly the brain, it is important to inquire about the presence of headache Nausea, vomiting, and drowsiness may also be manifestations of brain metastases A history of recent onset of a headache that has been rather persistent during the past few weeks or months and that had not been present previously is usually most significant Even though the roentgenograms of the skull and a most careful neurological examination are negative, the history of recent onset of a localized and persistent headache in a patient with bronchogenic carcinoma usually indicates cerebral metastases When such a headache is present, members of the patient's family should be questioned concerning any recent personality or behavior changes since these may be present in the absence of abnormal neurological findings An electroencephalogram may be helpful If the patient has had similar headaches prior to the last few months, no relationship need exist

When a patient with known or suspected cancer of the lung gives a history of localized recurrent pain of recent onset, metastases in that region must be strongly suspected Roentgenograms should be taken to demonstrate possible osseous involvement because bony metastases are not unusual with bronchogenic carcinoma. It should be appreciated

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nerve is not obviously in the region of the carcinoma. When a carcinoma of the lung involves the phrenic nerve in the upper half of the thorax, the mediastinal tissues usually show considerable invasion. If the pulmonary neoplasm is in the lower half of the chest and has infiltrated the phrenic nerve as it courses over the pericardium, partial pericardiectomy with the lung resection may still permit removal of the growth.

The roentgenogram of the chest should be carefully inspected for evidence of rib or other osseous destruction. If the patient gives a history of pain over the thoracic cage or vertebral column, spot roentgenograms of the suspected areas should be taken for bony detail. It should be appreciated that a rib may be extensively infiltrated by neoplastic tissue and yet appear normal even on the best radiographic examination. Moreover the anterior ends of the ribs are particularly difficult to visualize satisfactorily. The involvement of a rib by direct extension from an adjacent peripheral bronchogenic carcinoma has a different significance in relation to operability than when a distant rib shows a metastasis. When the involved portion of the chest wall is so located that it can be resected together with the pulmonary cancer, the lesion may still be considered operable (10). Most surgeons consider patients with a Pancoast syndrome caused by a lung cancer which has invaded the brachial plexus area as unsuitable for thoracotomy. Although radical surgical removal combined with radiation therapy with several years' survival in a few such patients has been reported, it is possible that a similar result might have been obtained by radiotherapy alone.

The lung fields should be carefully examined for possible metastatic or other nodules. Caution must be exercised in concluding that a second nodule is a metastasis. It might be an unrelated tuberculoma, benign tumor, or inflammatory lesion. If both lesions are on the same side, the presence of the second nodule, in itself, would not constitute a contraindication to thoracotomy. If the second nodule is in the contralateral lung, the decision hinges on the total evidence. Tomographs may aid in the decision by yielding further information concerning possible additional nodules. Rarely a second primary bronchogenic carcinoma may develop in the same or opposite lung after resection of the first lesion (Fig. 122).

When the neoplastic process visualized on the roentgenogram merges with the mediastinal shadows, and particularly if the patient gives the slightest history of dysphagia, barium studies of the esophagus are indicated. These may show varying degrees of displacement and narrowing of the esophageal lumen, but the esophageal mucosal outline usually remains intact. Although definite esophageal constriction or displacement by a bronchogenic carcinoma almost invariably means that the lesion

are shown to be metastatic foci. Conclusive radiologic evidence of distant bone metastases likewise contraindicates thoracotomy. Also the finding of a brain tumor of recent onset interdicts a thoracotomy except in special atypical circumstances.

When the total clinical picture strongly sugg... no positive pathol... consideration ... proce-dure consists ... pad of fat which overlies the lower portion of the anterior scalene muscle in the region of the clavicle. This fatty tissue with its contained lymph nodes can be removed under local anesthesia as a minor surgical procedure (21). It is usual to perform the biopsy on the same side as the pulmonary lesion The more anaplastic and more malignant the lung cancer, the greater the possibility that these lymph nodes will show microscopic evidence of metastases All of the excised "scalene biopsy" should be sectioned for pathologic examination since the neoplastic cells may be found outside the lymph nodes in some cases. The procedure is most likely to be helpful when there is a suspicion of paratracheal lymph node involvement on the roentgenogram

When the clinical findings suggest that the lesion may be inoperable but the diagnosis of cancer of the lung has not been definitely established, a more liberal viewpoint towards exploratory thoracotomy should be held The pulmonary lesion might not be the anticipated cancer and the suspected metastases might be due to an unrelated condition Hence each case must be judged on an individual basis

Determination of the Presence of Intrathoracic Metastases

The patient should be questioned concerning hoarseness of recent onset Paralysis of the left recurrent laryngeal nerve by a bronchogenic carcinoma in the hilar portion of the left upper lobe is not rare and usually, but not always, indicates an inoperable lesion. Occasionally the paralysis is caused by metastatic involvement of the mediastinum when the bronchogenic tumor is located elsewhere. It is important to distinguish an incidental finding of vocal cord paralysis at bronchoscopy in a patient who gives no history of recent change in voice from vocal cord paralysis, combined with a history of recent onset of hoarseness The former may be due to unrelated long-standing disease of the recurrent laryngeal nerve and therefore not due to cancer.

On fluoroscopic examination it should be noted whether there is any paralysis of the hemidiaphragm. Since diaphragmatic paralysis may occur from a variety of causes it should not be concluded that hemidiaphragmatic paralysis necessarily indicates malignant invasion of the phrenic nerve. This is particularly true if the diagnosis of cancer of the lung has not been proven histologically or when the paralyzed phrenic

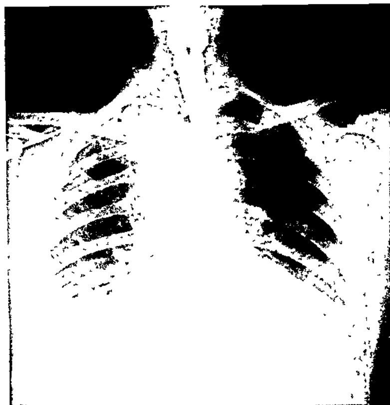


Fig 123 Esophageal displacement produced by the pulmonary lesion was assumed preoperatively probably to indicate mediastinal extension from a bronchogenic carcinoma At operation however the entire process was found to be due to actinomycosis which responded to chemotherapy This case emphasizes the need for exploratory thoracotomy when the diagnosis of cancer is unconfirmed

neoplastic cells When cancer cells have been definitely demonstrated in the fluid, an exploratory thoracotomy is usually not warranted

Radiologic evidence of definite hilar lymphadenopathy separate from the primary pulmonary lesion usually means that the patient will succumb to his cancer even though the surgeon might be able to remove the gross tumor tissue Bilateral mediastinal lymphadenopathy with a known cancer of the lung would not be benefited by exploratory thoracotomy unless there was a reason for suspecting that two separate disease entities were present Often the roentgen findings of hilar and mediastinal lymphadenopathy are only suggestive, and therefore should be regarded as unproven.



Fig 122 The nodule in the right upper lung field is a second primary bronchogenic carcinoma which developed two and one-half years after left pneumonectomy for bronchogenic carcinoma This second primary cancer in the opposite lung was successfully resected by segmental resection

cannot be completely removed by surgical means, it is important always to bear in mind that if a diagnosis of bronchogenic carcinoma has not been confirmed by pathologic examination, a similar esophageal displacement might be caused by a benign tumor or other lesions (Fig. 123).

Radiographic and clinical evidence of pleural effusion also must be interpreted in the light of other findings. If the presence of cancer has been proven in the underlying lung, an ipsolateral pleural effusion usually indicates a lesion beyond the stage of surgical curability. Pleural effusions due to infection distal to a bronchogenic carcinoma rather than due to pleural or lymphatic involvement by tumor are occasionally encountered. Bloody pleural effusion in the presence of proven bronchogenic carcinoma rarely is curable Pleural fluid should be examined for

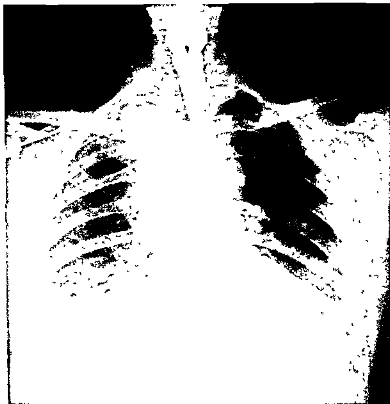


Fig 123 Esophageal displacement produced by the pulmonary lesion was assumed preoperatively probably to indicate mediastinal extension from a bronchogenic carcinoma At operation however the entire process was found to be due to actinomycosis which responded to chemotherapy This case emphasizes the need for exploratory thoracotomy when the diagnosis of cancer is unconfirmed

neoplastic cells When cancer cells have been definitely demonstrated in the fluid, an exploratory thoracotomy is usually not warranted

Radiologic evidence of definite hilar lymphadenopathy separate from the primary pulmonary lesion usually means that the patient will succumb to his cancer even though the surgeon might be able to remove the gross tumor tissue Bilateral mediastinal lymphadenopathy with a known cancer of the lung would not be benefited by exploratory thoracotomy unless there was a reason for suspecting that two separate disease entities were present. Often the roentgen findings of hilar and mediastinal lymphadenopathy are only suggestive, and therefore should be regarded as unproven

Bronchoscopic examination by an experienced endoscopist may give considerable suggestive information concerning the presence of mediastinal metastases. If the carina at the bifurcation of the trachea is markedly widened and the lower trachea and main bronchi are inflexible, extensive mediastinal metastases are almost certain to be found. Definite bronchial fixation usually means an inoperable lesion due to mediastinal metastases, but care should be taken not to confuse fixation of the left main bronchus due to tumor with relative inflexibility of the bronchus in that region due to an adjacent rigid arteriosclerotic aorta. The chapter on bronchoscopic examination contains a detailed discussion of endoscopic interpretation.

In evaluating the possible significance of intrathoracic findings it is again important to consider the clinical picture as a whole and not to decide that the lesion is certainly inoperable just because one of the findings that often or usually suggests inoperability is present. In borderline cases, and especially if there is a suspicion of upper mediastinal involvement, a scalene node biopsy or excision of some upper mediastinal connective and lymphatic tissue through a cervical incision may be recommended. If such tissue shows cancer, thoracotomy cannot be expected to demonstrate a truly operable lesion.

Angiocardiography has been employed in an attempt to assess more accurately the operability of a pulmonary cancer prior to surgical thoracotomy. By correlating the angiographic with the surgical findings it appeared that the lesions were almost always inoperable when occlusion of a major branch of the pulmonary artery at the hilum of the lung was demonstrated. Some workers believe such examinations are of considerable clinical value (22).

PREOPERATIVE EVALUATION OF THE PATIENT

If it is decided that surgical removal of the cancer of the lung is a possibility, the patient's general condition must then be assessed in relation to operative risk. Judgment in this matter should be somewhat flexible in that the possibility of the patient's deriving benefit from the surgical intervention must be considered in relation to the hazards involved. For example, in an elderly patient with poor pulmonary reserve who has apparently advanced cancer and little chance of complete surgical excision, it may be best to decide against exploratory thoracotomy. In contrast, a thoracotomy might be warranted in a younger patient with an apparently similar lesion but good general condition because the small chance of gain would not be offset by a comparable potential morbidity or mortality. Observance of inflexible rules which do not allow for individual judgment should not be applied to cancer surgery any more than to other fields.

Very few patients with bronchogenic carcinoma under 70 years of age need to be rejected for exploratory thoracotomy for conditions other than serious heart disease or marked emphysema. Rarely patients with other serious ailments may be rejected for surgical treatment. Severe hypertension is an uncommon observation in patients with bronchogenic carcinoma in my experience. Age in itself is no contraindication to operation. Many patients over 70 years old are suitable candidates for thoracotomy.

The most common problem in evaluation of operative risk encountered by the surgeon in the treatment of bronchogenic carcinoma is the question of pulmonary reserve, because of the frequency of pulmonary emphysema among patients with bronchogenic carcinoma. In deciding whether operation is feasible in a patient with a considerably diminished pulmonary reserve, both the immediate operative risk and the later pulmonary function must be considered. In this regard the surgeon must estimate the reduction in pulmonary function that will follow the surgical procedure. If the neoplasm by its location and extent has already caused complete loss of function of all the pulmonary tissue that will need excision, the ultimate function may be considered adequate if impairment of the function of the opposite lung is avoided. If, on the other hand, one is dealing with a peripheral carcinoma in a lung which has sustained practically no loss of function from the growth but where there is extensive bilateral emphysema with impending pulmonary insufficiency, the problem is obviously a very different one. Here naturally the amount of pulmonary tissue that is to be sacrificed at operation will enter into the estimated morbidity and mortality (Fig. 124).

Various tests of pulmonary function have been employed in the hope of making a better selection of patients for operation, and of lessening morbidity and mortality. Whereas such tests are of great value in the surgical management of certain patients with various pulmonary diseases, the experienced surgeon does not usually require special tests of pulmonary function in order to decide about the feasibility of exploratory thoracotomy in most patients with cancer of the lung. It is most important, however, that a very accurate history be obtained in regard to the presence or absence of dyspnea in the performance of everyday activity. This information can be of greatest value in estimating the possibility of postoperative pulmonary insufficiency. A history of even moderate dyspnea on exertion preoperatively should prompt the surgeon to be sparing in his sacrifice of pulmonary tissue, especially if this is possible with complete removal of the tumor. This subject is discussed at greater length in the section dealing with surgical technique, and in the chapter on pulmonary function.

Careful preoperative evaluation of the cardiac status is important par-

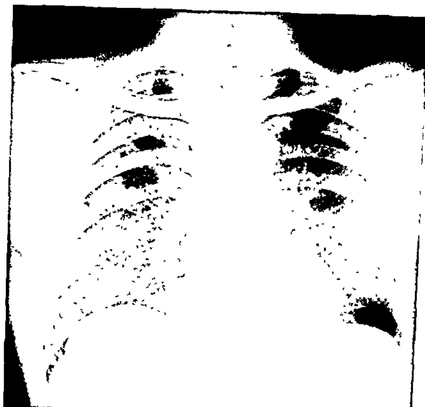


Fig 124 Roentgenogram of 63-year-old man with a bronchogenic carcinoma in the right midlung field The location of the neoplasm permitted either a lobectomy or pneumonectomy The operative findings indicated considerable pulmonary hypertension with emphysema, therefore lobectomy was considered the procedure of choice The degree of early postoperative dyspnea strongly suggested that a pneumonectomy might have resulted in a fatality Patients with pulmonary fibrosis and emphysema associated with extensive hilar calcifications may have considerable unsuspected pulmonary disability

ticularly in the older age group or when there is a history suggesting previous cardiac disability. The presence of persistent heart failure will usually be a contraindication to operation unless a response to medical therapy is obtained The possibility that a demonstrated cardiac abnormality may be due to neoplastic invasion of the pericardium and heart must also be borne in mind. Electrocardiographic abnormalities must be interpreted in relation to the clinical history and other findings A considerable percentage of patients with cancer of the lung who have abnormal electrocardiograms may be safely operated upon A history or electrocardiographic evidence of old coronary occlusion or auricular

fibrillation is in itself no contraindication to exploratory thoracotomy but in such patients great care in the operative and postoperative management is necessary. But similar precautions should be exercised in all cases since unrecognized cardiac defects may be present in any patient.

PREOPERATIVE PREPARATION

Most patients with cancer of the lung require little preparation for the operation other than the examinations to determine the indications for and feasibility of exploratory thoracotomy The patient with a small peripheral pulmonary tumor without significant secondary pneumonitis does not require chemotherapy prior to the day of operation In most patients with bronchogenic carcinoma, however, the neoplasm is located in a more proximal bronchus and there is usually secondary pneumonitis distal to the tumor even though the patient may have no signs or symptoms of this infection It is therefore wise to administer a broad spectrum antibiotic routinely in those cases for at least a few days prior to operation No time need be lost as a result of this preoperative preparation if the administration of the antibiotic is begun at the same time as the diagnostic procedures are started Moreover, this early use of the antibiotic may aid in the differentiation of a neoplasm from an entirely inflammatory pulmonary lesion When an undiagnosed nodule which might be either a neoplasm or a localized tuberculous lesion is to be explored, streptomycin or isoniazid should be given a few days before operation In a rare instance the patient with bronchogenic carcinoma, or more commonly one of the slower-growing tumors such as the bronchial adenoma, may have such extensive secondary suppuration with pulmonary abscess formation and excessive bronchial secretion, that even a few weeks of preparation with antibiotics is indicated

Since most patients with an operable bronchogenic carcinoma do not have marked anemia, weight loss or marked deterioration of their general condition, preoperative transfusion and other measures to improve the patient's general condition are usually not needed unless other diseases or deficiency states are present

ANESTHESIA

The importance of expert anesthesiology in the operative management of cancer of the lung is often not fully appreciated The surgeon who has an expert anesthetist on his team can obtain results that are not otherwise possible The rigid observance of certain basic principles by anesthetist and surgeon is more important than the exact type of anesthetic

agents employed *Adequate control of the airway at all times is mandatory* Sufficient oxygen should be given in order that there be a normal saturation of the arterial blood. There must be sufficient pulmonary ventilation in order to permit removal of carbon dioxide so as to avoid respiratory acidosis. At the time of this writing we have not yet routinely attained this goal, but mechanical ventilation with a positive and negative phase seems most satisfactory. The use of drugs which depress respiration should be avoided or reduced to a minimum. Ether has the advantage of stimulating respiration in spite of being a depressant to the central nervous system, but other agents are employed by many anesthetists Tracheobronchial secretions must be aspirated as soon as their presence is detected or even suspected Both surgeon and anesthetist must be aware of the hazard of clotted blood in the tracheobronchial tree.

Intratracheal anesthesia is recommended as a routine in pulmonary resection. The chief criticisms that have been directed against the use of intratracheal tubes during operation stem from the inexpert use of such tubes, and their advantages seem to outweigh by far the theoretical objections voiced by some This does not condone the inexpert traumatic introduction of an intratracheal tube. Care must be taken that the intratracheal tube is not introduced so far that it extends down into the right main bronchus and obstructs the gas exchange with the left lung. Special techniques of intrabronchial blocking have been employed by some, but are not a necessity except in certain unusual situations, such as in operations performed during active hemorrhage (which is rarely indicated) or when the operative procedure involves a resection of a portion of the trachea

The operative procedure should not be started until all evidence of satisfactory pulmonary ventilation is at hand. Much morbidity and mortality can be avoided if the operation is postponed for a week if serious ventilatory or circulatory disturbance occurred during anesthesia.

SURGICAL PROCEDURE

Surgical therapy in cancer of the lung consists of an exploratory thoracotomy which determines the feasibility of resection of the growth, with a pneumonectomy or lobectomy planned as the definitive procedure if the lesion is operable Although the operative procedure may be done with the patient in either the supine, lateral recumbent, or prone position, most surgeons today prefer the lateral recumbent position since this gives the greatest freedom of access to all portions of the hemithorax An anterior approach with the patient in the supine position is slightly better from the physiologic standpoint of respiratory disturbance dur-

ing operation but this may be more than offset by a less satisfactory exposure of difficult areas of dissection that may be encountered. If there is considerable deviation of the mediastinum to the left side, a left anterior approach is decidedly unsatisfactory because the displaced heart limits easy access to the lower portion of the pulmonary hilum. The



Fig 125 Photograph of patient showing scar of conventional posterolateral incision for pulmonary resection

prone position does not have the technical disadvantages of the supine position but its satisfactory employment necessitates a special operative table in order to lessen the respiratory difficulty which would result from the patient's lying directly with his chest on the table The author prefers the lateral recumbent position because it permits the greatest safety in dealing with any surgical difficulties that may arise, the slightly less satisfactory ventilation in this position may be adequately managed by an experienced anesthetist. The prone position on a special operating table has many firm adherents. During hemoptysis, such a position is desirable

In both the lateral and prone positions a posterolateral incision is employed which encircles the tip of the scapula (Fig 125). This incision

is made of sufficient length to permit adequate mobilization of the lower portion of the scapula, and access to the desired rib or intercostal space In operations for cancer of the lung where pneumonectomy is the most likely operative procedure, the fifth or six rib is usually resected for the widest possible opening in the midthoracic region. An intercostal incision is not desirable when a pneumonectomy is performed because it is more difficult to obtain an airtight closure with an intercostal incision The importance of a relatively airtight closure of the chest wall is considered further in the section on postoperative management. The opening into the pleural space should be long so that when the ribs are spread apart with the rib-spreader, there is little likelihood of producing additional rib fracture The surgeon may elect to divide an additional rib close to its vertebral end The author describes the present-day practice of opening the thorax with the realization that it is not completely satisfactory because of the high incidence of rather prolonged postoperative chest wall discomfort that it entails. This is especially true in the elderly patient with a rigid emphysematous chest.

After the pleural cavity has been adequately opened, exploration determines the extent of the neoplastic process and the feasibility of resection The most common pathologic finding which renders a cancer of the lung inoperable is direct extension of the neoplasm into the hilum of the lung so that the tissues around the pulmonary vessels are infiltrated When carcinoma surrounds the pulmonary artery in the mediastinum, the hazard of the surgical dissection is considerably increased and, even if a successful ligation of the artery is accomplished, later death from cancer is the usual result Therefore most surgeons regard such cases as inoperable. It should be emphasized, however, that the presence of discrete metastases in lymph nodes overlying the artery may not seriously interfere with dissection of the vessel and thus permit the lung to be removed. When the primary neoplasm or lymphatic extension from it encroach upon the pulmonary veins, intrapericardial ligation of these veins at the atrium may permit adequate control of the vessels (13) Some surgeons advocate routine intrapericardial dissection of the vessels, but most employ this technique only in cases in which the extent of the neoplasm dictates such procedure because of the increase in postoperative morbidity due to cardiac arrhythmias. Resection of a portion of the pericardium in continuity with the bronchus and lung does permit the surgeon to carry his dissection in a tissue plane slightly more distant from the growth than when a simple pneumonectomy is performed Whether such a more radical technique will lead to sufficiently improved results to justify its routine use, remains to be seen

When carcinomatous infiltration of the pulmonary hilum does not interfere with satisfactory isolation of the pulmonary vessels, but meta-

static foci seem to be present in the mediastinal lymph nodes or elsewhere, palliative resection may be considered. Before the lesion is deemed inoperable the surgeon must be certain that the lesions which are considered to be metastases are really cancer. Immediate pathologic examination by frozen section may be helpful.

If the lesion is considered operable, decision as to the extent of the operation must then be made. There is a justified difference of opinion between various surgeons as to the performance of routine radical operations for cancer of the lung, because it has thus far not been demonstrated that a very radical operation entailing a considerable increase in morbidity and mortality will lead to over-all improvement in total results. In most patients with cancer of the lung, a pneumonectomy is required if the lesion is operable. The extent of mediastinal lymph node dissection that is performed with the pneumonectomy varies widely (8).

In the surgical treatment of a cancer the importance of excision of the draining lymphatic channels into which the malignant cells may have spread has long been an accepted dictum. This same principle has been applied in varying degree to lung cancer. To what extent a dissection of the mediastinal lymphatics is feasible remains to be seen. Ample clinical and experimental evidence is available to indicate considerable crossing of the lymphatic drainage from one side of the mediastinum to the other. Thus the theoretical limitations of a unilateral dissection of the lymph nodes are apparent even though the centrally placed subcarinal group is excised. However, the final determination of the efficacy of various surgical procedures must rest on clinical results. Here again, the evaluation must be individualized on the basis of the type of cancer present. When final pathologic examination of a surgical specimen reveals involvement of the hilar lymph nodes but no evidence of extension to the nodes in the mediastinum, some five-year arrests of pulmonary cancer may still be obtained. When the mediastinal lymph nodes are also involved, a three-year survival is rare even if a radical mediastinal dissection has been performed. Thus the data available at present does not suggest that much increase in salvage can be anticipated by radical procedures in advanced cases.

Safety in pulmonary resection hinges on the careful dissection of the large hilar vessels. Adequate length for ligation must be obtained so that the large vessel is not divided close to a ligature which could then roll off. For maximum safety in the operative procedure the technique should be varied with the pathologic findings, with the general plan of ligating the pulmonary blood vessels first, and transecting and closing the bronchus as the last step. Some have advocated the early ligation of the pulmonary veins, in order theoretically to lessen the chance of blood-borne dissemination of tumor cells during manipulation of the

neoplasm in the lung (2). Secure closure of the bronchus is one of the most important requirements in lessening postoperative morbidity and even mortality. Although [illegible] opinions are still expressed, [illegible] apply· 1) There should be [illegible] supply of the tissues at the tip of the bronchus. Therefore stripping the bronchus bare of its peribronchial tissue tends to increase the possibility of bronchial fistula. 2) The number and type of sutures should minimize the ischemia of the bronchial stump. Simple sutures inserted through the cut end of the bronchus and tied just snugly enough to approximate the surfaces seem best to meet these requirements. Extensive mattress sutures may interfere with bronchial healing. Tacking a viable pleural flap over the sutured end of the bronchus or permitting adjacent mediastinal tissues to bury a bronchial stump is desirable. The smallest size suture material on the smallest needle that satisfactorily closes the bronchus without difficulty is preferable. 3) Although in general it is undesirable to leave a blind bronchial stump protruding from the trachea, the principle of high amputation of the bronchus should not be carried to the point where greater tension is then required to approximate the bronchial edges so that devitalization might occur.

PNEUMONECTOMY AND LOBECTOMY

The extent of the pulmonary resection in cancer of the lung is still a subject of debate but many surgeons are less rigid in their practice now as compared to a decade ago. At one time it was an accepted teaching in most clinics that anything less than removal of the entire lung which harbored a cancer was an inadequate surgical procedure. Further experience showed, however, that other factors than the amount of lung tissue removed greatly influenced the survival and rehabilitation rate a few years postoperatively In the majority of cases the carcinoma of the lung is so located that complete removal of the lung is necessary for adequate excision of the cancer In a significant percentage, however, the pulmonary lesion itself can be removed with an adequate margin by lobectomy. This particularly applies to the small peripheral lesion (Fig 126) The factors that should be given consideration in deciding between lobectomy and pneumonectomy in this latter group of cases are the following 1) the patient's cardiopulmonary reserve with special consideration of emphysema and possible pulmonary hypertension; 2) whether the diagnosis of cancer is certain, because a pneumonectomy performed for a unilobar benign lesion is a major error, 3) the probable type of cancer present, 4) the margin of apparently normal bronchus or pulmonary tissue between the cancer and the line of surgical transection, 5) whether the lobes of the lung are anatomically quite separate or whether a mark-

edly incomplete interlobar fissure readily permits crossed lymphatic drainage, 6) the difference in the line of bronchial transection between pneumonectomy and lobectomy of the involved lobe (the difference is less in the case of upper lobes), and 7) what the estimated difference of lobectomy and pneumonectomy will be on morbidity, mortality, and



Fig 126 Peripheral adenocarcinoma of lung in which resection of the right upper and middle lobes was performed

normal life activities It is obvious that judgment and the surgeon's philosophy about the role of surgery in cancer will influence the evaluation It is this author s opinion that lobectomy is the procedure of choice in many of the cases falling in the special group under discussion

Whenever a portion of the chest wall must be resected en bloc with resection of a mass in the lung, it is desirable that the pulmonary resection be limited to a lobectomy When a pneumonectomy is performed together with a large portion of chest wall, a considerable increase in morbidity and mortality must be anticipated because of the difficulty of main-

taining normal intrathoracic dynamics and a stable position of the med astinum in the early postoperative period.

When a bronchogenic carcinoma extends to the carina or lower trache most surgeons regard the lesion as inoperable. Some resections of suc lesions have been reported with operative survival by tracheal recor struction, but death from cancer has usually followed later (1)

During operation careful consideration should be given to the bloo replacement. Since blood from a blood bank is inferior to the patient own blood in a number of factors, surgical technique that lessens bloo loss during operation may reduce morbidity. It is best to start the trans fusion at the beginning of the operation and to replace the blood as i is lost in equivalent quantity Only a very small amount of saline solution such as is required to start the infusion at the beginning of the anesthesi before the blood is begun, should be given. If dextrose solution or salin solution except in minimal amounts is given during operation in additior to the blood, there is a considerable possibility that an undesirable amoun of intravenous fluid will be administered. Although the blood replacement should be adequate it is safer to err on the side of having the patient slightly underhydrated on the day of operation This applies particularly to the elderly patient with emphysema and pulmonary hypertension who is undergoing a pneumonectomy Overhydration is one of the factors in the production of excessive bronchial secretion during and immediately after extensive pulmonary surgery.

When a pneumonectomy is performed it is mandatory that the mediastinum be left in a relatively normal position at the end of the operation if the patient is to be least vulnerable to cardiovascular and respiratory difficulties in the postoperative period (16). A rubber tube drain should be left in the pleural space only while the chest wall is being closed in order that no undue amount of air can be trapped in the empty hemithorax during this time This temporary drain is removed at the completion of the skin closure and the patient is then placed in the supine position and a needle inserted anteriorly for the recording of the intrapleural pressure Careful manometric readings are taken and air is withdrawn or injected into the pleural space in order to leave a negative intrapleural pressure similar to that which one would estimate to be normal for that individual By this means the mediastinum will be brought into proper position. If there is any doubt about the accuracy of the intrapleural pressure readings because of the character of the patient's respiratory excursion, a portable roentgenogram of the chest is immediately made so that a median position of the mediastinal structures is known to exist.

Since some surgeons still employ drainage of the pleural space after pneumonectomy, the potential hazards and disadvantages of such a tech-

nique should be realized. Simple underwater drainage with water seal, such as is very satisfactory for a lobectomy, is highly undesirable after pneumonectomy and can contribute greatly to postoperative cardiorespiratory difficulties by causing marked mediastinal displacement. If pleural drainage is employed with a pneumonectomy, provision must be made so that an unduly negative pressure does not develop as air and fluid are forced out of the pleural space by coughing or straining. Therefore whenever the pleural cavity is drained after a pneumonectomy, the drainage setup should be so arranged that the degree of negative pressure which can be developed is limited in order to avoid undue mediastinal traction. The author also does not favor the insertion of a drainage tube which is occasionally unclamped in order to permit an undetermined amount of air or fluid to escape from the pleural cavity. Such a method may result in undesirable fluctuations in intrapleural pressure and mediastinal position from time to time. It is best to remove only that excess



Fig 127 Roentgenogram taken four days after right upper lobe lobectomy for neoplasm The excellent expansion with minimal pleural reaction is evident The middle and lower lobes were free of emphysema

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air or fluid from the pleural cavity which displaces the mediastinum. The drainage of the usual fluid from the pleural space after pneumonectomy is undesirable because the late mediastinal shift may thus be increased.

Some surgeons consider it desirable to produce a permanent paralysis of the hemidiaphragm at the time of pneumonectomy. Although the resultant more marked elevation of the diaphragm on the side of the pneumonectomy can undoubtedly decrease the size of the pleural space, undesirable sequels may also occur Marked elevation of the left hemidiaphragm may in occasional instances result in gastric symptoms due to displacement and rotation of the stomach It is uncertain whether ipsolateral diaphragmatic paralysis may be physiologically undesirable in the early postoperative period. The author has not personally employed phrenic paralysis with pneumonectomy. The diaphragm on the operated side may become considerably elevated within a few months after pneumonectomy even though phrenic paralysis is not induced.

When a lobectomy is performed the principles and technique of management of the pleural space are quite different than with pneumonectomy. When only one lobe of the lung has been resected, the aim is to fill the pleural space by expansion of the remaining lung tissue on the side of operation (Fig 127). Closed tube drainage, with or without suction, should be employed for this purpose. This drainage tube is usually removed from one to three days after operation at which time good expansion of the remaining pulmonary tissue should be present. Postoperative intrapleural manometric readings are not made after lobectomy

PALLIATIVE SURGICAL PROCEDURES

When exploratory thoracotomy reveals that non-resectable metastatic extension of the pulmonary cancer is present, consideration should be given to the feasibility and advisability of some type of palliative procedure The morbidity that the procedure might entail must be weighed against the palliation anticipated Too often extensive procedures fail to palliate because of the complications incurred. Foremost *in this latter* category is the resection of lung when neoplastic tissue must be traversed in the bronchial transection Bronchopleural fistula with its *attendant* morbidity and mortality is then likely to occur. In general it is unwise to cut through cancer tissue at the hilus The infection distal to the neoplastic bronchial stenosis can usually be ameliorated by antibiotic therapy after the thoracotomy, without lung resection Palliative resection of the lung is chiefly indicated when either a large necrotic *tumor*, repeated pulmonary hemorrhages, or severe pulmonary infection are present, provided the mediastinal metastases do not seriously *interfere* with a satisfactory hilar dissection Such cases are not common in the

author's experience In making this decision the surgeon should be guided by a thorough knowledge of what radiation therapy, antibiotics, and chemotherapy can offer in a palliative way for the type of patient and cancer under consideration.

When an inoperable pulmonary cancer with considerable pleural effusion is found at exploration, measures to lessen the need for thoracenteses in the future should be considered. This applies especially to those cases in which rapid reaccumulation of fluid is anticipated Since pleural effusion cannot occur if the pleural space is obliterated, fusion of the visceral pleura to the chest wall should be sought It is not necessary to achieve complete obliteration of the pleural space in order to lessen or eliminate the need for subsequent pleural aspirations If the lung becomes sufficiently adherent to the lateral chest wall so that it can no longer be collapsed against the mediastinum, massive fluid accumulations which displace the mediastinum are much less likely to occur Surgical attempts to obliterate the pleural space can only be successful if the lung can expand sufficiently to reach the lateral chest wall, perhaps with the aid of slight mediastinal shift toward the involved side The underlying principle is the maintenance of a roughened visceral pleura in contact with a rough parietal surface by closed drainage, preferably a simple water-seal type The visceral pleura may be irritated and roughened by gently rubbing with gauze. The chest wall side is rendered rough by stripping away and removing the parietal pleura over a large area of the costal surface The presence of metastatic nodules on the parietal pleura does not contraindicate the procedure, but does increase the likelihood of implantation of cancer cells into the thoracotomy wound The pleural drainage is maintained for several days and the drainage site then closed by tying a previously placed skin suture as the drainage tube is withdrawn If pulmonary expansion has been attained, persistent drainage is unlikely Such a pleurectomy at the time of exploratory thoracotomy still has a place in a few selected cases, even since the introduction of isotopes for malignant pleural effusions

In patients with a severe distressing cough but who have no significant bronchial infection and little sputum, vagotomy as a palliative procedure may be considered at the time that thoracotomy reveals an inoperable lesion The vagus nerve can be divided high in the thorax on the right side but below the branching of the recurrent laryngeal nerve on the left side Severe coughing spasms may be lessened by such vagotomy

When exploratory thoracotomy reveals a sizable pericardial effusion due to neoplastic involvement, pericardiotomy is indicated. A circular opening one to two inches in diameter should be cut into the pericardium so that the pericardial fluid may continue to drain into the pleural space postoperatively and thus avoid cardiac tamponade

Direct extension of a cancer of the lung into the adjacent chest wall is not uncommon. If the thoracic involvement is so located that resection of the chest wall and pulmonary mass can be done en bloc, the case is not considered inoperable. Too often, however, the site of neoplastic infiltration of the chest wall is located in the costovertebral region or at the apex of the thorax where en bloc resection with the involved lobe of the lung is not feasible. Although these non-resectable cases are the very ones in which severe pain may become a problem, nerve section is also often not feasible because the intercostal nerves are infiltrated by cancer close to their spinal origin. Thus intercostal neurectomy is only occasionally a feasible and helpful procedure in inoperable lung cancer. Those cancers located in the superior sulcus are usually the most painful group of pulmonary neoplasms. After radiation therapy no longer gives adequate relief, resort to neurosurgical procedures such as lobotomy and very high cordotomy must be considered.

Since the advent of antibiotics, surgical drainage of an empyema or a lung abscess distal to a bronchogenic carcinoma is rarely required. Such chronic suppuration is more likely to be seen in the slow-growing bronchial neoplasms like bronchial adenomas. If adequate control of the infection cannot be obtained by antibiotics, preliminary surgical drainage should precede the resection. An empyema may be associated with a resectable benign or malignant neoplasm.

Postoperative Care

The essential principles of postoperative care consist of a clear airway, adequate oxygenation, judicious sedation, and median position of the mediastinum. Rigid observance of these factors, particularly in the first few hours after operation, will do much to reduce the incidence of complications in later days.

With carefully performed surgery excessive bleeding during resections for carcinoma of the lung will be uncommon unless pleural adhesions are dense and vascular, or attempts are made to remove essentially inoperable lesions. With adequate replacement of blood, postoperative shock should be uncommon. Nevertheless moderate drops in blood pressure during the early postoperative hours are not uncommon. The clinical appearance of the patient is of great importance in evaluating the probable significance of a moderate hypotension. If the color is pink, respirations easy, the skin warm and the pulse slow, the prognosis is quite different than if cyanosis, dyspnea, and signs of vasomotor collapse are present. In either circumstance, however, one should make certain that the pulmonary aeration and mediastinal position are satisfactory. Restlessness and delirium following pulmonary surgery are usually due to hypoxia from some cause which must be corrected at once. Large doses

of narcotics at such a time are contraindicated and can prove fatal by increasing the unrecognized hypoxia.

It is essential that the tracheobronchial tree be cleared of secretion before the patient leaves the operating room If the airway has been kept properly free of accumulated secretions during the operation, a postoperative bronchoscopy is rarely necessary As soon as the patient regains consciousness he should be urged to cough, in order to clear the air passages Catheter suction of the pharynx and trachea must be utilized at the slightest indication of retained moisture in the tracheobronchial tree before the patient regains his cough reflex If the secretions are thoroughly removed early, the tendency for further secretions to develop will be less pronounced. Constant nursing care directed toward elimination of bronchial secretion is most essential If these factors are not thoroughly realized, the morbidity and mortality for pulmonary resection will be much greater than necessary If at any time later the secretions cannot be effectively evacuated by coughing, intratracheal suction must be employed. If this procedure does not adequately remove the secretions, bronchoscopy should be performed without delay Tracheostomy is indicated when secretions reaccumulate rapidly and cannot be satisfactorily removed by transnasal catheter suction supplemented by bronchoscopy. Such a situation can usually be avoided with proper preoperative preparation, adequate tracheobronchial suction during operation, and expert care in the early postoperative hours.

Early and adequate removal of bronchial secretion by effective coughing or tracheal aspiration will greatly reduce the incidence of postoperative pulmonary complications Patients with bronchospasm, asthma, and pulmonary fibrosis and emphysema are most difficult to manage Bronchodilators may be given systemically or by aerosol Expectorants may be of some help Broad spectrum antibiotics are used routinely after pulmonary resection Drugs are valuable but should not be regarded in any way as a substitute for effective mechanical removal of bronchial secretions

Pulmonary edema may occur due to excessive intravenous fluid administration, especially of saline solutions Edema of the lungs may result from partial airway obstruction either during or after operation Circulatory failure may also be responsible The patient with markedly reduced respiratory function is most likely to develop this serious complication Preventative measures such as avoiding hypoxia and excessive fluid intake, and maintenance of a clear airway, are far more effective than therapy of the established edema

Studies of the oxygen content of the blood after lobectomy and pneumonectomy have demonstrated that some reduction below normal in the per cent saturation is usually present for some hours or days after opera-

tion. It is therefore advisable to employ oxygen therapy after pul resection for one or two days In some cases with considerable sema or coronary insufficiency, fairly prolonged oxygen thera be advisable. In very severe emphysema the possibility of pr acidosis, delirium, and even coma with continued high per cent administration must be borne in mind.

The judicious use of analgesics in the early postoperative peri lessen the incidence of pulmonary complications If the patient's pain is not adequately lessened by a narcotic, respirations may shallow, and a deep effective cough may be impossible for some p On the other hand, large doses of narcotics which depress resp are also undesirable. It is best to give smaller doses at more fr intervals. Effective coughing should be particularly encouraged after an administered dose of analgesic has taken effect because tient's co-operation may be best at that time.

Attempts to lessen postoperative pain after thoracotomy by m nerve blocks with anesthetic agents, intercostal nerve section, and tions in the technique of opening and closing the rib cage, have m only partial success. Because of the great individual sensitivity as well as other factors, the comparison of the results with variou niques is beset by many variables Unless the surgeon personally views his patients in the weeks after operation, he may have an err impression as to the frequency and duration of such discomfort. the persistence or recurrence of the pain in the region of the i or often more anterior to it, even weeks after discharge from the h that is a particular nuisance Since similar postoperative discomfo lows thoracotomy in adults for non-neoplastic lesions, it is import assure the patient that it does not signify the development of a co tion. This author is unaware at present of any anesthetic agent for block which will be effective for the postoperative period and y entail the possibility of an even more distressing late neuritis

Following removal of an entire lung the anatomical readjustm quite different from that following lobectomy. Moreover the p logic maladjustments which may occur are of greater magnitud deserve special consideration Too little attention has been focus the details of management of the pleural space at the conclusion o operation and in the first few postoperative days. In contrast, the lems pertaining to the mediastinal displacement and overdistention o remaining lung which may occur slowly over a period of months or following operation have been the subject of considerable investig and discussion.

In few other situations can small differences in intrapleural pre have greater effects than at the conclusion of a pneumonectomy. Fo

ing removal of an entire lung the position of the mediastinum must be determined and controlled by regulating the amount of air in the space which remains after the lung has been removed (Fig 128) Since a displacement of the mediastinum will alter the volume of the remaining



Fig 128 Bedside roentgenogram one day after left pneumonectomy for carcinoma Note the satisfactory position of the mediastinum There is as yet little fluid in the left hemithorax which is largely filled with air

lung it is obvious that mediastinal displacement toward the side of operation will lead to acute overdistention of the remaining lung If, on the other hand, the mediastinum is displaced away from the side of operation, the remaining lung will have a reduced pulmonary volume Both situations are undesirable

The important role that mediastinal displacement, even of limited degree in certain cases, has in contributing to postoperative morbidity

and mortality after pneumonectomy, has been greatly underestimated. A number of factors have contributed to this state of affairs. The physiologic burden of an abnormal mediastinal position with its resultant effect on the ventilation and circulation of the remaining lung is insidious. It may take many hours or even days for the detrimental effect to become manifest In most instances the cardiac and respiratory complications which may develop are erroneously assumed to be due to primary disease in these organs. Animal experiments of a few hours' duration in which only certain gross measurements were made in normal dogs, led to a false impression of the clinical potentialities of acute thoracic displacements The effect of moderate degrees of mediastinal shift are far more significant from the standpoint of morbidity and mortality in the older age and poor-risk group of patients, than in those with a relatively normal heart and remaining lung. Therefore the cardiac arrhythmias, cardiovascular accidents, and occurrence of pulmonary edema may be considered incorrectly as inevitable sequels of the operation whereas they might not have occurred if the mediastinal displacement had been avoided. A failure to obtain obvious clinical improvement of cardiorespiratory function after correction of mediastinal deviation does not mean that it was not a contributory factor to the cardiovascular complication originally Except for immediately postoperatively, the position of the mediastinum cannot be accurately determined without the aid of radiologic studies. Whereas at the conclusion of the operation, before fluid in sizable amounts has transudated into the pleural space, intrapleural pressure readings can give a relatively satisfactory indication of the mediastinal position, this is no longer true when a hydropneumothorax is present (Fig 129). The generally higher morbidity and mortality following pneumonectomy which have been reported by surgeons who pay little attention to minute details in the adjustment of the mediastinum following pneumonectomy, tends sometimes to be incorrectly attributed to other factors such as accepting poor operative risks.

Cardiac arrhythmia may occur following pulmonary resection, especially in the older age group. The avoidance of mediastinal shift and hypoxia will lessen the frequency of this complication Treatment consists of correction of any mediastinal displacement, the use of cardiac drugs, and oxygen if hypoxia is present. When there is a sudden onset of auricular fibrillation, a bedside roentgenogram of the chest should be taken at once to determine the position of the mediastinum If even slight displacement toward the contralateral side is present, fluid or air should be aspirated from the pleural space. If the mediastinum has shifted to the side of pneumonectomy because of extrusion of air from the pleural cavity into the subcutaneous tissues, the intrapleural pressure should be recorded by a needle connected to a manometer, and some air should

be introduced into the pleural cavity. If the auricular fibrillation is at a rapid rate, as is usual at its onset, digitalis is usually indicated Quinidine or pronestyl may also be given with proper caution.

Tachycardia may be caused by a variety of conditions which include



Fig 129 Same case as Fig 128 Roentgenogram a week after left pneumonectomy shows the normal gradual increase in fluid in the space from which the lung was removed The mediastinum has remained in the midline because air has been absorbed as the fluid has increased

mediastinal displacement, hypoxia, pulmonary complications, and acute gastric dilatation Gastric dilatation should be relieved by insertion of a tube through the nose into the stomach

Ambulation within the first few days after operation is desirable Leg exercises can be employed while in bed Thromboembolic complications are less frequent after pulmonary surgery with good postoperative care than following most other major surgical procedures

Wound complications after pulmonary resection for cancer should be very rare Bronchopleural fistula, which used to account for a significant

percentage of the postoperative morbidity and mortality, should now also be a rarity, but the surgeon and his staff should ever be on the alert for the signs of such a complication. If a patient who has had a pneumonectomy suddenly begins coughing up bloody fluid, a bronchopleural fistula should be suspected at once. Unless the technique of bronchial closure has been grossly unsatisfactory, bronchial fistula usually does not develop in the first few days after operation but is more likely to occur about five to ten days postoperatively. The presence of a bronchopleural fistula is confirmed by comparing the expectorated fluid with the character of fluid aspirated from the pleural space, and by intrapleural pressure readings after evacuation of the fluid. Whenever a postpneumonectomy bronchopleural fistula is even suspected, the patient must never be placed so that the fluid-containing pleural cavity is uppermost, because serious or even fatal aspiration into the tracheobronchial tree or other lung may occur. The author strongly advocates immediate aspiration of fluid followed at once by open thoracotomy so that the pleural cavity is emptied and remains so. He has seen several deaths result from inadequate drainage with a closed thoracotomy in the presence of a fair-sized bronchopleural fistula. Thoracoplasty and myoplasty are indicated later unless the bronchial fistula closed spontaneously.

Operative Morbidity and Mortality

The surgical literature indicates a considerable variation in the morbidity and mortality associated with lung resection for neoplasms. Although there has been considerable improvement in recent years, particularly as regards the mortality from pneumonectomy, much room for improvement remains. The fact that certain individual surgeons have been able to show consistently lower complication rates than encountered in many hospitals cannot be discounted by assuming that such surgeons do not accept poor risks. Individualizing the type of surgical therapy is important in the author's opinion. Also meticulous attention to the factors discussed under operative and postoperative treatment can influence the results to a greater degree than is generally appreciated. During a 12-year period the author's hospital mortality for pulmonary resection for neoplasm has been slightly less than 4 per cent. The hospital death rate for thoracotomy in inoperable cases has been 1 per cent. The attitude toward the extent of intervention in advanced cases of cancer has been conservative. The operative mortality rates of certain other surgeons are given in the discussion of surgical results later in this chapter.

Procedures for Mediastinal Displacement after Pneumonectomy

Since the mediastinal shift to the side from which the lung was removed may, over a period of months or years, gradually cause cardiopulmonary

difficulties in some patients, means of avoiding such displacement have long been sought. Although thoracoplasty has been most widely employed for this purpose, it has several drawbacks An additional operative procedure is often required as it increases the operative risk if done



Fig 130 Roentgenogram one month after right pneumonectomy for adenocarcinoma in a 32-year-old woman Note the complete opacification of the right hemithorax due to the normal filling of the hemithorax with fluid after pneumonectomy Later there was more displacement of the heart to the right side

concomitantly with pneumonectomy in an elderly patient with lung cancer The thoracoplasty may further reduce pulmonary function by disturbing the mechanics of the chest cage If scoliosis develops, dyspnea may occur To overcome these disadvantages of thoracoplasty, various prostheses have been inserted into the pleural space None thus far have proven ideal At present the tendency in most clinics is to await the result of the pneumonectomy done for lung cancer, and to observe the patient for cardiorespiratory symptoms since it is now appreciated that many tolerate the readjustment surprisingly well (Figs 130, 131) The

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Fig. 131 Roentgenogram ten years after left pneumonectomy for lymphosarcoma Patient was asymptomatic and had no dyspnea

patients who develop difficulty because of tracheal angulation and esophageal displacement have usually had the right lung removed Occasionally extreme displacement may occur (Fig. 132). In such an instance, thoracoplasty is definitely indicated and will usually cause definite symptomatic improvement unless the symptoms were due to pulmonary emphysema

Surgical Treatment of Pulmonary Metastasis

When a solitary mass which appears to be a neoplasm is discovered in a roentgenogram of the lungs, the possibility of either a primary pulmonary cancer or a metastasis to the lung from an extrapulmonary site must be considered The characteristics of bronchogenic carcinoma have been described in various chapters of this book but it has also been indicated that at times a clinical differentiation between a primary and a secondary growth may be impossible. When the patient has previously been treated for a cancer in some other organ or part of the body, the suspicion that

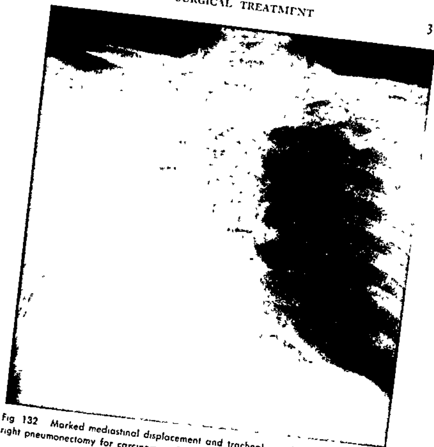


Fig 132 Marked mediastinal displacement and tracheal angulation one year after right pneumonectomy for carcinoma This was corrected by a thoracoplasty

the pulmonary mass is a metastasis is naturally great Yet the occurrence of another primary cancer in a person who has previously been successfully treated for one neoplasm is not rare The incidence of multiple primary cancers in the same individual was studied by Cahan *et al* (7) In 1493 cases of lung cancer there were 25 multiple primary cancers in which the lung was the site of one of the tumors The most common sites for other primaries associated with lung cancer in this Memorial Hospital series were oral cavity, skin, and larynx, but a very wide variety of other primary sites has been reported Therefore it must not be assumed that a nodule in the lung of such a patient is necessarily a metastasis Since surgical excision of a solitary pulmonary metastasis is occasionally beneficial, pulmonary resection, preferably lobectomy or even a more limited resection, may be advisable in such situations

When the weight of evidence strongly indicates that a pulmonary mass is probably a metastasis, the likelihood that a "cure" can be obtained by any surgery is very small. In order not to subject patients with metastatic pulmonary cancer to useless operations, various criteria may be employed to select those few cases in which resection might be of benefit, realizing that exceptions will occasionally occur. Criteria for considering pulmonary resection of a lung metastasis are one or more of the following: 1) uncertainty as to whether the lung lesion is primary or secondary, 2) the pulmonary mass is solitary, 3) especially when the mass is of fairly large size and still solitary; 4) tomographs in posteroanterior and lateral projections show no other masses in the lungs, 5) slow growth of lung mass, 6) considerable time has elapsed since primary cancer was eradicated, 7) no evidence of neoplasm at primary site or outside of lung; 8) low-grade malignancy of primary growth—sarcoma more favorable



Fig. 133 Large tumor mass in left lung was considered to be a primary pulmonary neoplasm Patient was well for five years when a brain metastasis developed Autopsy demonstrated that primary lesion was a carcinoma of the adrenal

than carcinoma, and 9) a tumor of atypical or unpredictable behavior (Fig 133)

A review of the reported cases of pulmonary resection for metastatic lesions prior to 1949 was made by Seiler *et al.* (19) About two-thirds of the lesions were carcinoma and one-third had metastatic sarcoma Considering the relative frequency of the two types of neoplasm, a higher percentage of solitary sarcomatous metastases are favorable for resection and almost half of the late survivors reported by Seiler had sarcoma The most common primary tumors encountered among the surviving group were fibrosarcoma, hypernephroma, carcinoma of the colon and rectum, and of the ovary.

Surgical Treatment of Rarer Types of Bronchial and Pulmonary Cancer

In the surgical treatment of most primary cancers of the lung the principles determining the extent of resection are similar although there is a recognized difference in the success of the therapy as applied to various pathologic types In the management of tumors of low-grade malignancy, however, some variations in surgical approach may be both feasible and desirable Therefore individual consideration will be given to the surgical treatment of the rarer types of pulmonary neoplasms

The carcinoid type of bronchial adenoma should be treated by the most conservative type of resection which permits complete removal of the growth (Fig 134) If the tumor can be resected by a lobectomy, this is the procedure of choice (23) When the carcinoid bronchial adenoma is so located that a lobectomy is unsuitable, consideration should be given to a bronchial resection with plastic repair in order to avoid a pneumonectomy Such a localized resection may be combined with lobectomy. If suppurative disease has caused irreversible changes in the lung distal to the tumor, a conservative resection may not be feasible

The cylindromatous type of bronchial adenoma should usually be treated by pneumonectomy unless tracheal extension interferes with that procedure Very few cylindromas occur sufficiently peripheral to permit resection by lobectomy Lymph node dissection should be combined with the pulmonary resection Radiotherapy should be employed if surgical removal is incomplete

Sarcoma primary in the lung is usually treated by types of surgical resection similar to carcinomata Because of their rarity, insufficient data are available to assess the relative merits of radical versus more conservative resections in the management of lung sarcoma (18) Rapid growth prior to operation does not necessarily have the usual unfavorable prognostic



Fig 134 Bronchogram demonstrates a filling defect in the right main bronchus below the upper lobe orifice due to a bronchial adenoma Because of the nature of the neoplasm, middle and lower lobe lobectomy rather than a pneumonectomy was considered the procedure of choice although the tumor is not far distant from the upper lobe orifice

connotation (Fig 135). The possible advisability of postoperative radiotherapy must be considered in this group Radiation treatment is certainly indicated if recurrence is manifest

Bronchiolar or alveolar cell carcinoma requires special consideration from the surgical standpoint as well as in diagnosis because of its peculiar

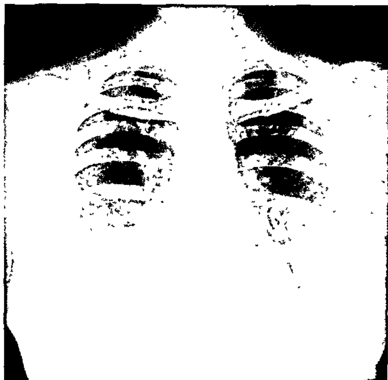


Fig 135 Reticulum cell sarcoma of right middle lobe Patient well three years after lobectomy

growth characteristics Storey *et al* (24) have made an extensive analysis of the literature Since different authors have varying criteria for designating a particular case as one of alveolar cell carcinoma, comparison of the reports from different clinics is often confusing Therefore it is as yet impossible to define accurately the spontaneous behavior of such tumors Storey concluded that conservative pulmonary resection would seem to be the treatment of choice in the majority of patients Views on the prognosis with surgical therapy vary depending on the type of cases included in this special pathologic category (Fig 136).

Churchill *et al.* (9) reviewed the cases of carcinoma of the lung treated at the Massachusetts General Hospital from 1930 to 1950. A clinical diagnosis was made in 1130 patients and confirmed histologically in 681. Thoracotomy was done in 294 cases, and a resection carried out in 171 (25.1 per cent of proved cases, 58.2 per cent of patients explored); 114 had pneumonectomy and 57 lobectomy. Of these, 137 survived resection (20.1 per cent of patients in whom the diagnosis was established histologically). The pneumonectomy mortality rate was 28.7 per cent prior to 1948 but only 3.7 per cent in 1948–1949. Likewise the lobectomy mortality dropped from 22.6 per cent to 3.8 per cent. Six of 48 patients lived five or more years after pneumonectomy, and four of 21 were alive five or more years after lobectomy. Of 29 patients without involvement of lymph nodes, 34 per cent survived five years. None with lymph node involvement survived five years (which differs from reports of other clinics). This Massachusetts General Hospital report does not include those cases with bronchial adenoma.

Moore (17) analyzed the cases of carcinoma of the lung at the Presbyterian Hospital in New York during the ten-year period ending in 1949. Of the 370 patients, 42 per cent were explored, of these 56 per cent underwent resection. Only 13 per cent of the resected cases survived five years or more.

The surgical aspects of bronchogenic carcinoma as seen in a general hospital are indicated by the statistics reported from the New Haven Hospital (4). In a series of 300 cases, 59 per cent were considered inoperable without exploration. Of the 40 per cent explored, a resection was performed in slightly over one-half, which constituted 21.3 per cent of all admissions with proven bronchogenic carcinoma. Less than 5 per cent of all the patients with lung cancer survived five years.

Boyd *et al.* (5) reported on 403 cases of carcinoma of the lung treated at the Lahey Clinic. Resection was performed in 25.8 per cent of the total cases seen, but only 9.5 per cent of all cases survived five years or longer. The total resection mortality was only 7.6 per cent, and 37.8 per cent with a "curative resection" survived five years or longer.

Gibbon *et al.* (11) reported on 380 cases in which an exploratory operation was done. In 205 a resection was performed, 190 had a pneumonectomy. The operative mortality of patients who underwent extirpation was 22 per cent. The five-year survival rate was 22 per cent for patients whose cancer was removed.

MacManus *et al.* (15) reported on 199 exploratory thoracotomies for carcinoma of the lung performed from 1947 to 1953. The three-year survival rate for patients leaving the hospital alive between 1947 and 1950 was 22 per cent.

Taylor and Waterhouse (25) report that of 1147 patients subjected to

pneumonectomy by different surgeons in Great Britain, 52 7 per cent had survived one year, 33 3 per cent two years, 23 9 per cent three years, 18 7 per cent four years, and 13 7 per cent five years In patients without lymph node involvement the five-year follow-up shows 25 to 35 per cent survival figures

Brea (6) of Argentina reported on 880 cases of bronchogenic carcinoma. Thoracotomy was performed in 311 cases and resection in 200 of these The operative mortality was 22 per cent for pneumonectomy and 4 8 per cent for lobectomy Fifty-eight patients were alive at the time of the report, of these 34 were living more than two years after operation

Barthel (3) of Hamburg, Germany, reported on 195 patients with carcinoma of the lung out of a total of 450 upon whom resections were performed (174 pneumonectomies and 21 lobectomies) Sixty-six died during or shortly after operation Two-thirds of the discharged patients died within six months Such statistics suggest that many patients with advanced disease were subject to resection

Sellors (20) reported an analysis of 689 thoracotomies performed for cancer of the lung between 1940 and 1950 A resection was performed in 446 patients Forty per cent were alive at the end of two years and 34 per cent at three years The five-year survival rate was 21 per cent

The important influence of the cell type on the prognosis of bronchogenic carcinoma is well demonstrated by the analysis of the data from the Mayo Clinic reported by Kirklin *et al* (14) They classify their cases of bronchogenic carcinoma into four groups with the following incidence

Squamous cell carcinoma	33 7%
Adenocarcinoma	12 6%
Small cell carcinoma	15 8%
Large cell carcinoma	37 9%

(The relatively small percentage listed as "squamous cell carcinoma" in this series is due to the authors' rather strict criteria of epidermoidization, many cases that others might classify as "undifferentiated squamous carcinoma" have been placed in the "large cell carcinoma" group in which the cells are not forming squamous elements or glandular elements) Their analysis of these various types of bronchogenic carcinoma in relation to percentage explored, resectability with view to cure, and five-year survival was as follows

	% Explored	% Resected	% 5 Yr Survival
Squamous cell carcinoma	58 5	34 1	11 8
Adenocarcinoma	47 5	25 8	11 0
Small cell carcinoma	36 4	11 6	0 8
Large cell carcinoma	46 0	19 6	5 0

The poor resectability rate and the dismal five-year survival rate in small (or oat cell) carcinoma are again documented. Although the five-year survival rate of adenocarcinoma in the Mayo Clinic series is almost as good as their results with squamous carcinoma, it should be pointed out that there is a rather marked variation within the former group. The mucus-producing adenocarcinoma and papillary adenocarcinoma, which are subgroups, may have a better survival rate than the remainder of the adenocarcinomas. In none of this discussion has the bronchial adenoma or cylindroma been included because of their very different behavior and prognosis. The Mayo Clinic nine-year survival rate for adenoma of the bronchus was 84 6 per cent. It is easy to see how inclusion of even a small number of these slow-growing tumors (although justifiably listed as adenocarcinoma, Grade 1) with the other bronchogenic carcinomas gives a completely misleading impression as to the prognosis of the common type of bronchogenic cancer. In the Mayo Clinic series 7 6 per cent of the primary cancers of the lung were adenomas of the bronchus This is higher than the incidence would be in unselected material. It should also be mentioned that the five-year survival rates of the Mayo Clinic cannot be compared with those of a general hospital in which there is much less selection of cases. Institutions known for their surgical work may receive a higher percentage of referred cases in which surgical therapy may still be considered a possibility. The writer in his own experience has noted a striking difference in the types of cases with cancer of the lung which he saw in a cancer hospital, a municipal hospital, a general voluntary hospital, and a surgical clinic Data gathered from any one of these are not representative for the problem of lung cancer in the general population as far as operability or late survival rates are concerned. But the Mayo Clinic data as cited above gives a true picture of the relative res

Some reports in recent

of their more peripheral

apparently in the Mayo series are included in other categories. Only 1.2 per cent of the lung cancers of the Mayo Clinic were classified as alveolar cell tumor

The effect of lymph node metastases on the five-year survival rate in bronchogenic carcinoma is also important. Thus far there have been extremely few three-year survivors when the mediastinal as well as the hilar lymph nodes were involved, even though a radical mediastinal dissection with pneumonectomy was performed When the hilar lymph nodes contain metastases but the mediastinal lymphatics are not apparently invaded, a small percentage of five-year survivors may occur with pneumonectomy or occasionally even with lobectomy. However, there is a sharp drop in even the three-year survival rate when the hilar lymph

nodes show metastases, and only a few live five or more years. Similarly, resection of the chest wall or diaphragm which is invaded by direct extension from the lung only occasionally results in long survival, but still is occasionally indicated

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13

Radiotherapy in Lung Cancer

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AND BERNARD ROSWIT

GENERAL CONSIDERATIONS

It is our task in this chapter to discuss the contributions that ionizing radiation can make towards the welfare of patients with surgically incurable carcinoma of the lung While the proportion of resectable cases varies somewhat throughout the country, it is a conservative estimate that at present three out of four patients with carcinoma of the lung coming to the physician are already beyond hope for surgical cure Further, of those patients with resections, about two out of three will not have been cured by that procedure and will either present evidence of local recurrence or distant metastases

It is apparent, therefore, that the radiologist today faces an obligation for providing nonsurgical treatment for many patients with bronchogenic carcinoma Radiation treatment may play a role in assisting patients with this disease at various stages, from the relatively early lesion in some patients unsuitable for surgery, to the patient with widespread metastases and a relatively short life expectancy

We share the opinion of Smithers (50) that radiation therapy can relieve their suffering and disability in a way that is not possible at present by other means Yet it is still not made sufficiently available to all who may need it Too many general practitioners, remembering the past, when radiation sickness was commonplace and local reactions were severe, seem far too ready to deny their less debilitated patients the benefits of present radiation treatment (50)

PALLIATIVE RADIATION THERAPY

What can the radiologist do for symptomatic patients harboring an advanced intrathoracic lesion or distant metastatic disease? By the time they reach the radiologist, their condition precludes any serious attempt at prolongation of life Nevertheless, our principal role as physicians is

to relieve suffering and disability in these individuals, despite their ... life expectancy. They are surely ...
humanit...
dise.

Clinical Benefits

Relief can be offered to more than 50 per cent of these patients by means of conventional radiotherapy, and with relatively little discomfort arising from the use of ionizing radiation. Our combined experience in the management of more than 1500 patients with this disease has convinced us that we can offer respite from chest pain, productive cough, hemoptysis, dyspnea, orthopnea, bone pain, impending paraplegia, dysphagia, and the clinical syndrome associated with obstruction of the superior vena cava. The improvement thus gained may last from several weeks to many months. This experience is shared by nearly all clinical investigators reporting on this problem including Allison (1), Brooks and his colleagues (2), Craver (7), Dobbie and Livingston (9), Felton (13), Haas (18), Harvey (23), Hilton (24), Leddy (32, 33), Mayer (38, 39), Smithers (51), Tenzel (54), and Widmann (61).

Objective evidence of satisfactory radiation response is characterized by restoration of pulmonary aeration (Fig. 137A and B), improvement of respiratory function, regression of pulmonary infiltrates, shrinkage of involved lymph nodes (Fig. 138), and restoration of neurological competency. Probably the greatest single advantage of ionizing radiation lies in its ability to re-establish bronchial drainage. Suppuration distal to the obstructing tumor produces symptoms which dominate, harass, and shorten the patient's life.

An osseous metastasis in the lumbar spine threatening to produce paraplegia or creating severe pain, clearly presents an immediate therapeutic problem and can be greatly helped by radi...
sees restoration of bony architec...
137C and D). It is of particula...
metastases can be aided, because this frequent complication is psychologically so distressful and constitutes a severe drain on the family and the community because of round-the-clock nursing care that is frequently necessary.

Although the superior vena cava compression syndrome is an ominous complication, it is here that the therapeutic radiologist performs his most outstanding service. In 75 per cent of such cases, the strangulating edema of the upper respiratory tract, cerebral anoxemia, and other manifestations, can be promptly and strikingly relieved for relatively long periods. Of particular therapeutic significance is the high incidence of anaplastic



Fig 137 *Results*

A A 63-year-old white male with proven epidermoid carcinoma, Grade II, received treatment directed to the carina through anterior and posterior 10 × 10 cm ports A tumor dose of 6000 r was delivered in 39 days, using a 1-Mev machine This film shows the situation prior to treatment Note the massive atelectasis in the right lung with compensatory emphysema of the left lung

B This film was taken three days after completion of treatment, and shows clearing of the right lung, except at the base

C A 40 year-old white male was treated for epidermoid carcinoma of the right upper lobe, proven by exploratory operation This film was taken for planning purposes at onset of radiation and shows partial destruction of the second rib as well as the tumor density The lead markers and drawn lines relate to orientation of treatment portal The patient was treated with telecobalt, 6500-r tumor dose being delivered in 37 days

D This film, taken five months after completion of treatment, shows recalcification of the second rib There is some pulmonary fibrosis in the right upper lobe, but no evidence of tumor



Fig 138 The Superior Vena Cava Compression Syndrome *

A Angiocardiogram before treatment in 51-year-old white male with anaplastic epidermoid carcinoma of the right upper lobe bronchus Patient was critically ill and in great distress with dyspnea, orthopnea, swelling of head and neck, and clinical evidence of extensive collateral circulation Note obstruction of superior vena cava at a point below the junction of the right and left innominate veins No opacification of the superior vena cava is noted, but extensive collateral circulation is visualized, including huge left cardiodiaphragmatic vein

B Angiocardiogram in same patient after tumor dose of 2660 r, followed by a six months' remission Recurrence was again treated with tumor dose of 2800 r with remission of additional two months Note the marked reduction of visualized collateral channels, with opacification of the superior vena cava

(radiosensitive) lesions reported in this group (49). The pathologic physiology of this syndrome in bronchogenic carcinoma has been fully described elsewhere by one of the authors (B R) (49)

X-ray therapy is unequivocally the treatment method of choice, providing much longer remissions than nitrogen mustard, without the toxic complications of the latter In fulminating cases, a daily tumor dose of about 75 r is suggested for the first few treatments Total regression of the tumor mass may be seen after a tumor dose of less than 3500 r. The response to nitrogen mustard is usually prompt but of very shor duration In critical situations, when roentgen therapy is not immediately available or feasible, nitrogen mustard may be effectively employed in conventional dosage as a prelude to radiation treatment.

Histology and Response

Some undifferentiated bronchial tumors are so radiosensitive as to simulate lymphomas in their response The first evidence of clinical benefit

* From Roswit, B , Kaplan, G., and Jacobson, H G. "Superior Vena Cava Obstruction Syndrome in Bronchogenic Carcinoma," *Radiology*, 61:722, 1953. Courtesy Charles C Thomas, Publisher, Springfield, Illinois.

in such cases may be noted as early as a few days after initiation of treatment The gratifying regression of these anaplastic lesions and the uniformly poor results from surgery in oat cell carcinoma have prompted Smithers to suggest that apparently operable cases be treated by radiation methods alone (51). However, one cannot overlook the discouraging fact that anaplastic tumors spread so rapidly that four out of five will sooner or later have blood-borne metastases The well-differentiated epidermoid carcinomas are as radioresponsive as squamous cell carcinomas in other internal organs The adenocarcinomas may be unexpectedly responsive to radiation but the alveolar cell lesions have rarely been influenced.

TREATMENT METHODS

Palliative benefits will generally be satisfactory with a tumor dose of approximately 3000 r in three to four weeks, employing conventional radiotherapy apparatus and techniques The dosage in each new patient must be individually considered, on the basis of sound clinical and radiological judgment In extrapulmonary lesions it is sometimes well to compress the treatment time to the shortest over-all period compatible with achievement of a successful result These patients have no time to waste For example, an intractably painful skeletal lesion may be treated with a tumor dose of 3000 r in two weeks rather than in four weeks

The available clinical evidence strongly suggests that an even higher tumor dose to the primary lesion and regional nodes will provide improved immediate benefits as well as longer remissions. At any dose level, the planning, prescribing, and delivering of effective roentgen therapy always demands painstaking care and skill The casual administration of "just a few treatments" will almost invariably result in failure to benefit the patient

In many cases, a pair of opposing portals, or a three-field technique, including the volume of the primary lesion and regional nodes, may be the most feasible because of the large tumor volume (Fig 142A and B) A lead-rubber grid (12, 21, 36) can be quite helpful in avoiding untoward skin reactions, but the dose to the skin through the open areas ought not to be carried much above 15,000 r (Fig 139A) A multiple portal cross-firing plan is most desirable whenever attainable but rotation therapy is currently regarded as the optimal method with conventional apparatus (Fig 139B, C) Rotation affords an almost infinite variety of treatment plans including scanning, in combination with fixed portals (Fig 139D)

We do not regard supervoltage radiation as essential in palliative treatment of this disease Nevertheless, in our experience, the single most valuable measure for reducing local and systemic complications and making greater palliation available to more patients has been the introduction



Fig 139 *Conventional Treatment Techniques*

A Lead-rubber grid employed with conventional (260-Kev) machine for minimizing skin damage, thus allowing delivery of more intensive radiation to deep-seated neoplasm ("poor man's supervoltage method")

B Multifield crossfire treatment utilizing light beam localizer, plastic in pointer steel back-pointer, and resin-plaster treatment shell for maximal precision and daily reproducibility of beam alignment

C Complete rotation (360°) with 260-Kev-treatment machine, providing the advantages of an infinite number of crossfiring portals

D Rotational setup for the scanning technique (180°) Note resin-plaster shell for immobilization of the patient and for support of the required wax bolus in an area of irregular contour

of one to three Mev radiation (Figs. 140A, 140B, 141A). The clinical and physical advantages of this modality will be further discussed. Haas (18), Harvey (23), and Watson (58) feel that very high energy radiation in the betatron range (22–30 Mev) may further improve results while minimizing further the side effects of radiation, both local and systemic (Fig 141B).

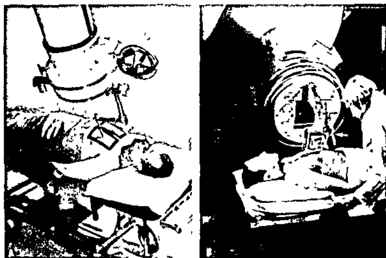


Fig 140 *High Energy Treatment Techniques*

A One million volt crossfire treatment Note precision beam director designed by one of the authors (B R), providing accurate and reproducible beam orientation in each of two planes

B Two million volt x-ray generator for multi-portal therapy of deep seated lesions Note precision devices, including light localizer plastic cone and pin-and-arc unit (Courtesy of Francis Delafield Hospital, New York City)

Selection of Patients

Each patient has the right to be considered as an individual when he is referred for an opinion as to roentgen therapy He ought not to be made the captive subject of a "project" or bound by a rigidly standardized treatment policy In patients with marked cachexia, overwhelming disease, or advanced age, treatment should be generally withheld Necrotizing peripheral lesions, without access to a major bronchus, usually do poorly The rare alveolar carcinomas have not responded, nor have we often been successful in controlling recurrent pleural effusion The management of intractable fluid accumulation by means of radioisotopes will be discussed in another chapter If a target symptom or specific



Fig. 141.

A Cobalt^{60} Teletherapy Unit providing high energy radiation at relatively low cost, with minimal local and systemic reactions

B Twenty-two-Mev treatment utilizing x-rays from the betatron The outstanding characteristic of x-rays of this energy is the skin-sparing action, maximal ionization occurring 4 cm below the surface.

lesion has shown no evidence of improvement by the time 3000 r (tumor dose) has been delivered, there is no point in pursuing more aggressive radiotherapy Treatment of patients with the Pancoast syndrome is usually difficult and unrewarding, particularly with conventional energy levels (200–260 Kev). However, with high tissue doses (5000–6000 r), made feasible with 1 Mev or more, gratifying symptomatic and objective response can be seen (Fig 137A, B) Occasionally recalcification in ribs partially destroyed by cancerous invasion has even been achieved (Fig 137C, D).

GENERAL MANAGEMENT

Whenever possible, patients receiving radiation therapy should be managed on an out-patient basis in order to keep them associated with their families as long as possible To this end supportive measures such as control of anemia, improvement of nutritional status, control of infection, and prevention of mental depression, are all beneficial measures which today should be routine in management of these patients The details of this aspect of radiation treatment of the patient have been adequately considered by other authors (38, 39, 44).

This objective should not prevent the admission of a patient to the hospital when his over-all condition is such that the remaining time at home is no longer pleasurable and profitable to himself and to his family. Thus the patient under management for his malignant disease, who con-

tinues to be anemic, malnourished, weak, and listless will usually benefit little by attempting to stay at home while receiving radiation In our opinion he will be less likely to be benefited by radiation During hospitalization, his nutritional and other systemic needs will be adequately supplied, thus providing improved tolerance towards the required treatment course

RADICAL RADIATION THERAPY

What can the radiologist do for patients with early bronchogenic carcinoma—operable and apparently resectable? So long as therapeutic radiologists rarely get to treat such patients it will remain impossible to reach a satisfactory conclusion about the value of radiotherapy in the cure of this disease It is well recognized, however, that stage one squamous cell carcinoma in other sites is a radio-vulnerable disease. There is no reason to believe that stage one squamous cell carcinoma arising in the bronchus sharply modifies this general observation.

What of the operable patient in good general condition whose lesion proves to be non-resectable, either because of the extension of the primary lesion, or of fixed regional lymph nodes? This is a problem encountered in about one out of four patients who reach the physician It is our belief that in these individuals prolongation of useful life through early, well-planned intensive radiation is a realistic and attainable objective. Although the number of well-documented favorable reports is still small, radical therapy continues to gain wider support in many clinics both here and abroad (1, 2, 5, 13, 15, 18, 19, 23, 24, 38, 41, 50, 51, 54)

An attempt at cancerocidal treatment is justifiable in the inoperable patient with minimal symptoms, because the best time to control cancer is when it is first recognized—not later. Just as in malignant disease elsewhere, radiation is far more likely to control small tumors than bulky ones Brooks and his colleagues report that of the 126 non-resectable cases radically treated, 18 4 per cent survived from two to five years (2) Smithers notes that of 192 inoperable cases receiving radical treatment, 12 4 per cent survived two to seven years after treatment (50) On the other hand, untreated patients will not often survive more than two years after the diagnosis is established.

It is important to indicate that in the past, with the techniques then at hand, aggressive treatment of lung tumors was rarely feasible Severe, acute skin reaction most frequently prompted termination of treatment Treatment schedules were unduly prolonged, thus diminishing tumor response, according to current concepts of optimal time-dose relationship

Radiation sickness of greater or lesser severity was encountered in two out of three cases (11), sometimes proving an obstacle to completion of

the treatment course. In recent years, radiological advances have paralleled the remarkable progress in thoracic surgery. Utilizing to full advantage improved equipment as well as knowledge in radiobiology, radiation physics, rotational techniques, supervoltage radiation, and new chemotherapeutic adjuncts, the radiologist today is well prepared to explore fully the possibility of more effective treatment in carcinoma of the bronchus.

Complications

It is the tolerance of the normal lung itself which remains today the critical limiting factor to be considered in any realistic effort to destroy the local lesion and its regional nodes. Radiation fibrosis of the lung is not a frequent symptomatic complication, but it can be greatly debilitating. However, successful resections of fibrotic lobes have been reported (3, 4). The possible contributions of agents capable of modifying the reaction of normal lung tissue to radiation will be discussed below.

With conventional radiation in the 200–260 Kev range and portals of moderate size, the skin will show evidence of a smart erythema involving moist desquamation at approximately 3500–4000 r (skin dose). Such patients are sometimes peremptorily withdrawn from the radiotherapy schedule by alarmed practitioners who refer to this tissue reaction as a "burn." With the simplest of hygienic management during the acute phase, this complication will subside soon after completion of the treatment course.

When supervoltage radiation is employed, only a mild erythema or bronzing is seen, even after skin doses approaching 6000 roentgens and employment of large skin portals. Radiation sickness is no longer a serious obstacle to radical therapy, since the advent of steroid and chemotherapy (10, 37). In fact, patients treated with supervoltage radiation in our clinic rarely complain of this syndrome.

Dosage Levels

Existing knowledge is far from complete concerning the optimal relationship between tumor dose and treatment time that appears most likely to control the local malignant disease. Available evidence suggests that for epidermoid carcinoma in other primary sites, it may lie between 5000 and 6000 r in five to six weeks. As one approaches these intensive schedules, treatment by conventional methods (200–260 Kev) becomes increasingly difficult and fraught with greater hazard to skin and other normal tissues. Lead-rubber grids (12, 21, 27, 34, 36, 52), multiportal crossfire plans, and rotational techniques (17, 20, 53) have served to minimize these risks. However, with supervoltage radiation, it becomes possible to deliver the desired dosage to most deep-seated lesions with

relative ease, shorter time schedules, and minimal local and systemic reactions Telecurie therapy equipment, utilizing cobalt 60, provides radiation equivalent to that of a 2 Mev x-ray apparatus When utilized with rotation units, with the patient in a horizontal position, radical therapy may be greatly facilitated (15). Examples of typical treatment plans are illustrated in Fig. 142

Treatment Planning

Although treatment techniques are carefully individualized for each patient, a general pattern of management may be briefly described An effort is first made to localize the site of the primary lesion and regional nodes as precisely as possible, utilizing every available radiologic method In this connection, the thoracic surgeon can be of great service to the radiologist, if he "pins" the definable margins of non-resectable disease by means of metal clips or radon seeds The exact body contour in the principal horizontal plane of the tumor is made with a quick-drying resin plaster bandage strip and traced on a centimeter-ruled planning sheet The landmarks of tumor and important anatomic structures are drawn in on the life-size cross-section pattern

The maximum, minimum, and average tumor doses are then prescribed, including the range of over-all treatment time, in days The upper limits of permissible dosage to critical normal structures are then clearly stated The determination of the physical factors now to be employed (portals, angles, quality, etc) is largely the outcome of applied radiologic physics, utilizing available isodose charts for the radiation quality on hand. The result may represent a simple treatment plan of paired-opposing portals (Fig 142A) or multiple crossfiring beams (Fig 142B), rotational or scanning technique, a supervoltage plan (Fig 142C), or telecurie therapy (Fig 142D).

Whenever possible, one should utilize the advantages of mold technology Individually constructed shells of quick-drying resin plaster bandage (Fig 141B) provide opportunity for three-dimensional treatment planning, absolute immobilization of the patient, and precisional portal orientation—easily reproducible throughout the treatment course For application of wax bolus or protective lead barriers, the plaster shell is indispensable (Fig 141D). Radiographic confirmation of accuracy of beam alignment is obtained Special devices for precise beam alignment are utilized, including directors (8, 45), pin-and-arc, and back-pointers (41) (Figs 141, 142)

During the course of therapy, evaluation of clinical, radiologic, cytologic, and histologic response is secured regularly and recorded The treatment schedule may be modified according to the integration of these factors as well as the patient's systemic reactions.

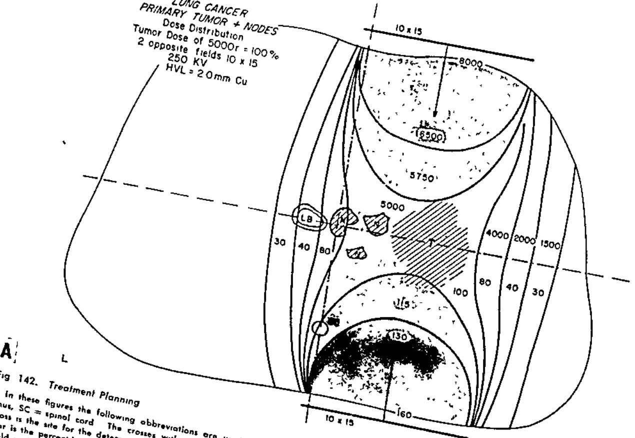
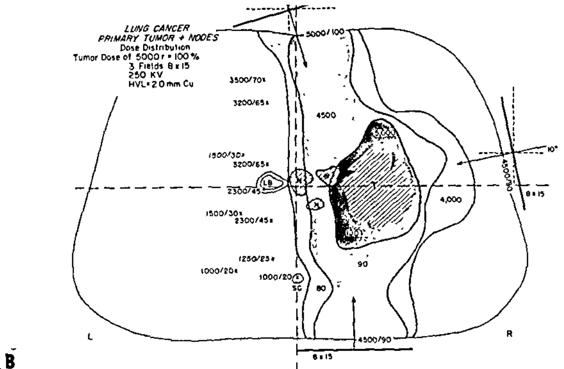


Fig 142. *Treatment Planning*

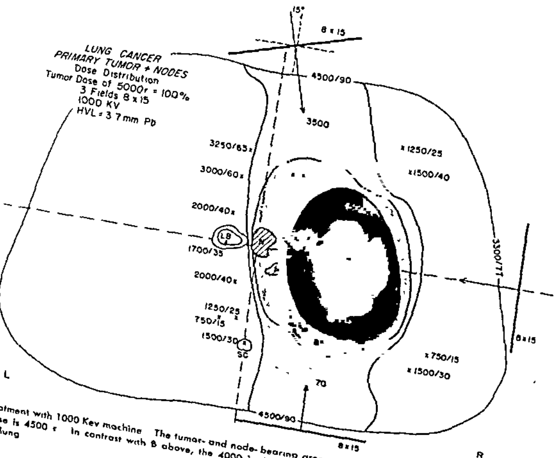
In these figures the following abbreviations are used: T = tumor, N = lymph nodes assumed to have secondary tumor deposits, LB = left bronchus, SC = spinal cord. The crosses with which are associated a number, a bar, and a second number are to be interpreted as follows: the cross is the site for the determination of the energy deposition in roentgens, which is given by the number before the bar. The number after the bar is the percentile figure for that number divided by the maximal tumor dose which in each instance, is 5000 r. The angle associated with a field is the angle that that field presents to the horizontal or vertical axis of the patient. The size of the field is indicated next to the heavy line by two numbers. The area of the field may be obtained by multiplying these two numbers.



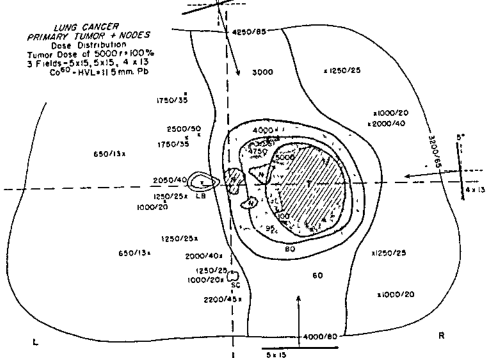
B

A A two field technique (paired-opposing portals) has three major disadvantages 1) *low tissue dosage* coupled with high skin dosage, 2) the "wasp-waisted" contour of *the isodose lines*, resulting in areas of inadequate deposition of energy in the tumor site Note that one node lies well outside the 5000 r line, 3) excessive volume dosage to normal lung tissue

B This figure shows the Improvement in tumor/normal tissue ratio associated with the addition of *a third or lateral* field to the two-field technique in Fig 142A



C Three-field treatment with 1000 Kev machine. The tumor- and node-bearing areas now range in energy deposition from 4250 to 5000 r. Maximal skin dose is 4500 r. In contrast with B above, the 4000 isodose line has moved centrally, diminishing the volume deposition in the homolateral lung.



D Three-field dose distribution outline with the cobalt[60] unit The field sizes are somewhat smaller because there is considerably more penumbra from this cobalt unit than from the I-Mev machine By convention the 90 per cent isodose line is used for specifying field size The maximal skin dose has been reduced slightly (4250 r) The nodes and the tumor-bearing area are all contained in the 4000 to 5000 isodose area

PROSPECTS FOR THE FUTURE

It is recognized today that the patient with widespread metastases from cancer of the bronchus when first seen, or who develops these after surgical treatment of his intrathoracic disease, cannot be cured by any current therapeutic means. Further, no reasonable extrapolation of these techniques offers future prospect of cure.

If widespread disease is to be treated successfully with radiation, it seems necessary to develop a method for selective localization in cancer cells of a parenterally administered material acting as a carrier of a radioactive agent. Realization of this principle is in the indefinite future. Possibilities under investigation at the fundamental level include *first*—the utilization of the antigen-antibody response. This assumes that cancer specific antigens can ultimately be isolated and made to convey a radioactive barb. A *second* concept assumes that it will be possible to find, or make, compounds similar to the fluorescent dyes that will localize selectively in tumor cells Such compounds would then be used to carry the nuclear radiation to the tumor cell.

A *third* possibility assumes that there may exist other elemental concentration mechanisms similar to the iodine-thyroid mechanism. Studies currently under way determining the concentration of trace elements present in a wide variety of normal and tumor cells will ultimately tell us whether or not this is so If so, then exploitation of a physiologic mechanism analogous to the thyroid's ability to concentrate radioiodine will be possible

While these studies continue at the *fundamental* level, clinicians will observe them with keen interest and will utilize their developments when possible Meanwhile, what can be said regarding developments in the *immediate* future that might reasonably be expected to lead to an improved ability to help patients with this disease? The answer to this question might be divided into these general categories. 1) changes in equipment used to generate the therapeutic beam of radiation directed to the tumor, 2) combined external and internal radiation methods, 3) possibility of combining surgical or chemotherapeutic attack with radiation, and 4) possibilities for significantly modifying the reaction of the normal tissue or enhancing the response of the tumor tissue to a given amount of ionizing energy.

1 It is our belief that the more widespread utilization of generators of x-rays and telecurie therapy units in the 1–3 Mev range will improve our ability to assist the patient with disease confined to the thoracic cavity In general, as the energy of the beam of ionizing radiation is increased within certain limits, there is an improvement in our ability to deliver the desired dose to the volume believed to contain the tumor.

This is so because the ratio of that energy to the energy deposited in the surrounding normal tissue is improved This fact carries with it the corollary that the systemic effects of radiation, which may be a limiting factor in the execution of the treatment plan, are sharply diminished For example, a plan of treatment may call for 6000 r to a reasonably large volume. An attempt to deliver this dose with conventional radiation will usually fail to be completed because the patient may not tolerate the total amount of energy which must be deposited in his body to deliver 6000 r to the volume containing the tumor

With high energy radiation, the skin tolerance is markedly improved because maximum ionization now takes place well below the skin surface. In this connection, the betatron (22–30 Mev) offers the greatest advantage to date with maximum ionization 4–5 cm below the epidermis

Whether types of radiation other than photons (x-rays) will represent an advance in our ability to help patients with carcinoma of the lung, is far from clear at the present time. A type of radiation currently being therapeutically tested in a limited number of centers is the electron beam generated either by betatron, synchrotron, or linear accelerator There is no theoretic reason to anticipate a sharp biological difference in response from that already seen with photons, since fundamentally the exchange of energy between a photon beam and the patient depends upon the production of electrons within the patient Thus, if one uses electrons from the first, it is difficult to see how this will result in any sharp biological difference in response However, the physical properties of electron beams, in contrast to photon beams, are such that they have a finite range that is a function of their energy, and thus may be expected to produce some practical changes It has been shown in preliminary studies that the radiation from an electron beam, in tissue substitutes, is virtually homogeneous from the surface of the tissue substitute, i e, the skin, to the maximal range of the electron beam Thus it is possible to irradiate a block of tissue with substantially no deposition of energy outside that block of tissue This is in contrast to the photon beam which, to a first approximation, deposits its energy exponentially throughout the patient

Whether the electron beam can be utilized to the great advantage of patients with carcinoma of the bronchus is not yet clear to us In our opinion, the anatomic location of cancer of the bronchus makes it unlikely that the electron beam will come to play a major role in the management of these individuals

Even farther into the future is the utilization of positively charged particle beams in distinction to the electron beam, which is composed of negatively charged particles Examples are beams of protons, deu-

terons, or alpha particles Here again, the anatomic problems of distribution presented by this malignant disease make it unlikely that great advances will be associated with improvement of the art of using these beams in the treatment of human cancer.

Thus, in the past, our attention has long been concentrated on improvement in the source of ionizing radiation; this was the facet of the problem obviously in need of improvement, and furthermore, could be improved. As equipment became more powerful, the ratio of energy in the tumor cell to the normal cell improved. This has resulted in slow but steady progress in our ability to treat successfully patients with cancer This phase of the art, we believe, has largely reached its end. For the foreseeable future we have probably gained the maximal benefits that are to be obtained by concentrating our attention on the sources of external radiation.

2 Radiation to the tumor also may be given by combining external radiation with injected or insufflated radioactive elements or compounds (46) Examples include instillation of colloidal radioactive gold, silver-coated radiogold, or radiophosphorus into the bronchus, or injection of larger particles of these radiomaterials via the pulmonary artery to a selected segment of the lung. Direct interstitial implantation of radon seeds and other radioactive agents into the tumor mass and involved nodes also can be accomplished. The chapter on radioisotopes discusses these methods in detail. The principle here is to increase the dosage to the tumor and regional nodes, while attempting to spare the surrounding normal structures as much as possible.

3. The prospects for a combined effort by differing therapeutic modalities should be mentioned. One of these is combined surgical and radiation attack on lesions whose operability is borderline. By means of vigorous radiation prior to surgery, a certain fraction of this group may be converted into surgically accessible tumors Wood was successful in five out of 11 such cases (63). Hare (19) and others are making a similar effort, utilizing 1–2 Mev therapy This approach, in our opinion, deserves to be explored in an orderly and systematic fashion by other clinics Experimentally a variety of chemotherapeutic agents including nitrogen mustard and its derivatives, 6-mercaptopurine, 8-azaserine, N methyl formamide, and derivatives of urethane, have been used in combination with radiation. Some investigators have reported encouraging results (28, 48) Since the concept of attempting to injure the cancer cell by two mechanisms simultaneously is an attractive one, more studies of this type may be expected in the future.

Clinically the use of nitrogen mustard prior to radiation has already found a place, as discussed above, in the management of superior vena caval compression (49).

In addition, in certain patients with severe systemic manifestations, nitrogen mustard has served to make local radiation therapy feasible in otherwise hopeless situations (48). Judicious clinical investigation may develop other useful combinations of chemotherapeutics with radiation.

4. The question of modifying the response of the patient to ionizing radiation is a facet of radiation therapy which has been largely unapproachable until very recently. Fundamental studies show clearly that the response of biological systems to x-ray beams is a modifiable phenomenon and is in part dependent upon the chemical environment of the cell. One factor is the amount of available oxygen in or around the cell at the time of exposure to x-rays. Other effective agents are of a diverse chemical nature, among them, potassium cyanide, cysteine, glutathione, and ethanol have been shown also to modify response. The relationship of their effects to the oxygen effect is not yet clear.

Recently, tools with which to investigate and manipulate the response of the cell being radiated have been given us by the biologists. The only organized attempt at the clinical level to modify patient response that has come to our attention is the work done by J. S. Mitchell (40) at Cambridge University, who has been exploring in an orderly fashion the role of possible radiation sensitizers of the tumor cell as a means of potentiating the efficiency of radiation in damaging the tumor cell in cancer of the bronchus. This work is still in a very early phase from the clinical point of view, and final judgment cannot be reached at this time as to the merits of the family of sensitizers under clinical trial at Mitchell's department. Preliminary analysis appears to show modest prolongation of life in the patients receiving these agents simultaneously with radiation treatment. Lanier has made similar observations with other agents in experimental tumors (31).

Whether or not these particular compounds will modify radiation response is not so important as the fact that the response to radiation has been shown to be a modifiable system. If it is a modifiable system, continued work and diligence will ultimately give us clinical tools with which either to reduce the sensitivity of the normal tissues surrounding the carcinoma of the bronchus, or to enhance the sensitivity of the carcinoma cell itself. Perhaps it is not too much to hope that by judicious exploitation of anatomic and physiologic considerations, it may be possible to utilize both phenomena simultaneously.

Where this most exciting and promising field will lead us is impossible to say. It is possible, however, to draw upon prior experience in medicine and state with considerable conviction, that whenever a new set of facts has been given us regarding a therapeutic situation, it has invariably led to improvement, sometimes in a striking way, of the effectiveness

with which we can apply that therapeutic modality to the problems presented to us by our patients. There is no reason to feel that this general principle will not obtain in bronchogenic carcinoma. When it will obtain is a matter for conjecture. It will depend upon the difficulties presented to us by the application of the principle, and upon the diligence and perception with which interested investigators pursue its application.

There is another facet of modification of radiation response of the normal tissue which deserves brief mention. It has been known for a long time that the parenchyma of the lung is one of the more sensitive tissues to ionizing radiation. The injurious response is basically that of an inflammatory process which, passing initially in most cases through an exudative phase and progressing to a fibrotic phase, may finally be associated with respiratory physiologic dysfunction (6, 14, 59). This has been in the past one of the real hazards of curative efforts in management of carcinoma of the lung. Limitations of space do not permit us to discuss this facet of patient management in great detail. Here, again, is a real challenge to radiation biologists and therapeutic radiologists. Can this process be modified? Since the most troublesome aspect is essentially one of an organized inflammatory reaction, the question resolves itself to a rather fundamental one of modification of a nonspecific reaction of the body to an insult. Attempts have been made to modify this reaction by the introduction of cortisone or ACTH since in other settings it is known to diminish the body's reaction to a wide variety of insults by diminishing the response of connective tissue (6, 16).

It is yet too early in the investigative phase to evaluate fully the evidence as to whether cortisone does significantly decrease the probability of the development of postradiation pulmonary fibrosis. Similarly, cortisone is being studied in an attempt to reduce existing radiation fibrosis. Other lines of attack with this and other agents deserve to be explored. If this process can be significantly modified, then one of the critical limiting factors in radiation control of the primary lesion, and of the metastatic regional nodes, will be partially removed.

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14

Radioisotope Therapy in Lung Cancer*

Bernard Roswit

GENERAL CONSIDERATIONS

The radioactive isotopes have proved helpful in the management of patients with *inoperable bronchial cancer, relieving suffering and disability* and prolonging useful life In this chapter we shall review the rationale and indications for the use of these agents, the technical factors to be employed, the clinical advantages to be expected, and the possible risks involved

Useful clinical applications of radioisotopes in the treatment of this disease have thus far remained limited in number and scope This is largely due to the physical and biological limitations of these agents, the restrictions imposed by the anatomic spread of disease, and the paucity of fundamental research in this area. In view of the present meager probability for cure in bronchial cancer, it is hardly surprising that investigators in nuclear medicine have focused their attention on more fruitful studies in other primary sites of malignant disease. Nevertheless, the growing need for palliation in a high proportion of the cases continues to challenge the imagination and skill of some experimental workers in this field

The palliative benefits of *external* radiation have been shown to improve with an increase in the dose delivered to the intrathoracic tumor, but not without the risk of trauma to intervening normal lung It would appear advantageous, therefore, to enhance these benefits through the further development of *internal* radioisotope therapy The selective localization of intensive nuclear radiation to specific lung segments and to regional nodes has recently been accomplished by a variety of physical

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methods. The potentialities and limitations of this approach will be critically reviewed on the basis of recent knowledge in this field

INTRAPLEURAL THERAPY

When intractable pleural effusion complicates the course of bronchogenic carcinoma, the patient's suffering is aggravated by dyspnea and greater restriction of useful activity. Repeated attempts at aspiration of the pleural space are distressing. The persistent loss of fluid, electrolytes, protein, and sometimes blood, further burdens the patient's survival period. We have not been too helpful with external radiation sources, utilizing conventional or supervoltage x-rays in our clinic.

Clinical Benefits

Intrapleural injection of radioactive gold (Au^{198}) in colloidal suspe sion has been effective in controlling fluid accumulation in approximate 50 per cent of the cases This method was first suggested by Hahn (1- 15) and introduced clinically by Muller (38). When the treatmen proves to be useful, there is a marked slowing of fluid accumulation In the most favorable cases, there is complete cessation of all fluid formation for the remainder of the patient's survival period, associated with distinct improvement in general well-being. For example, of 112 patients receiving radiogold for intractable pleural effusion of malignant origin (lung, brain, and ovary), Moses, Kent, and Boatman (37) report excellent resu in 48 patients (no further taps), and reduction of effusion in 12 ca (one or two subsequent taps) Of 47 patients with bronchogenic carc noma mentioned in this report, 22 achieved excellent results and fi were improved No consistent difference in response was noted, dependent upon whether the primary was in the lung, brain, or ovary. The number of encouraging reports from other clinics has been steadily mounting (Andrews and his colleagues (2, 3); Clark and LeRoy (8); Kent and Moses (26, 27), King, *et al* (30), Seaman, Sherman and Bonebrake (47), Storaasli, *et al* (49), Walter (52), and others)

Biophysical Considerations

The half-life of Au^{198} is 2 7 days with emission of beta particles (average energy 0 32 Mev), and gamma ray (0 41 Mev). Practically all of the radioactivity is dissipated before the end of two weeks The colloidal gold employed is nontoxic, insoluble in body fluids, and relatively inert biologically. It gives rise to none of the immunological or skin reactions encountered with soluble gold salts. The radioactive material is injected intrapleurally in the form of a cherry-red colloid suspension, with particles measuring approximately 20–200 mμ in size. This agent tends

to flocculate on the pleural membrane in the majority of cases, and may be found lodged there in the macrophages. Practically no radioactivity is noted in the regional lymph nodes and insignificant fractions may be detected in the peripheral blood and urine. Post-mortem studies have revealed a mild diffuse radiation pleuritis, with variable degrees of fibrous pleural thickening. Adhesions may become extensive, creating numerous fluid pockets (2, 3).

Although a variety of etiologic factors has been advanced to explain the malignant effusion, substantial proof for any single cause is lacking. It has been suggested that fluid may arise from the presence of numerous tiny implants of cancer on the pleural surface, from impairment of venous and lymphatic drainage by tumor cells, or through perversion of the normal dynamics governing transfer of fluid across the pleural membrane. Current investigations with tritium and other radioactive tracers may provide an answer to this intriguing question. In any event, the beta irradiation arising from the tiny flocculated particles of radiogold appears adequate for suppression of fluid formation. Whether this is the outcome of the shallow irradiation of tumor cells, the small blood vessels, or the pleural membrane itself, is not entirely clear. The underlying lung is functionally preserved because the maximum range of the beta particles is only 3.8 mm. in water or tissue. Ninety per cent of the energy is dissipated within the first millimeter. Although the far more penetrating gamma ray component of Au^{198} contributes less than 5 per cent of the radiation effect on the serous membrane, it constitutes a hazard to patient and personnel through total body radiation.

SELECTION OF PATIENTS

Patients best suited for a trial of intrapleural radiocolloid include those who experience distress from the fluid accumulation and whose probability for survival will be long enough for them to enjoy the benefits of this palliative measure. Few physicians have the omniscience to predict with accuracy the survival time in any individual case. Nevertheless, this treatment should not be given in the few remaining days or weeks of an obviously terminal period, or in patients who are very rapidly becoming worse. The presence of malignant disease as the origin of the effusion should be histologically or cytologically established before considering intrapleural therapy. It has been shown that radiogold is of no value in tuberculous patients with pleural effusion, nor has it been effective, according to animal studies, in subjects with ascites due to cirrhosis, or in congestive heart failure (37).

Patients with bulky intrathoracic tumors are more suitable for external roentgen therapy. When the pleural fluid is grossly bloody or contains considerable fibrin sediment, much of the colloid may become enmeshed,

with little practical benefit to the patient. Lavage of the pleural space in such cases has been undertaken just before the introduction of the radioactive colloid (46).

When there is suggestive evidence that multiple pocketing of fluid has occurred, it is unwise to introduce radiogold for fear of producing profound radiation effect in a very limited area. A preliminary radiation survey of the chest wall, after injection of a tracer amount, will serve to obviate this risk, the gamma radiation supplying a convenient tracer. It may be well to consider taking serial fluid samples after tracer injection, to assist in selecting those patients in whom the radiomaterial is promptly flocculated on the pleural membrane. It has been our experience that this agent may sometimes fail to deposit on the serous surface, even after several days. It is obvious that use of intrapleural radiogold therapy in such patients would be futile.

Some have questioned the value of administering Au^{198} in patients with minimal fluid and little symptomatology (37). However, it is desirable that other groups fully explore the potentialities of "prophylactic" therapy. In a few clinics, Au^{198} is introduced in the postoperative period after pulmonary resection, with the hope of destroying floating cancer cells or tiny pleural implants (27, 42).

TREATMENT METHODS

After aspiration of most of the fluid, the agent may be introduced by any one of a variety of well-established techniques. The patient is required to change position at frequent intervals for about three to four hours after the injection. We have sometimes utilized an automatic rocking-bed for this purpose. The dosage varies from clinic to clinic, ranging from 75 to 150 millicuries per instillation, and is based largely on empirical clinical experience. This may be followed by more treatment after several weeks if indicated. It is well to remember that in some cases there will be considerable lag between the administration of the radioisotope and the cessation of fluid formation. Repeated doses totaling 450 millicuries have been given to some patients in an effort to stem the tide of rapid reaccumulation. There is yet no adequate method for calculating accurately the pleural dose in rads, because of the great variations in colloid distribution and in pleural surface area.

Several different mechanical systems for intrapleural injection have been suggested (2, 3, 42, 48, 51). In our own laboratory, an apparatus has been devised which appears to be simpler and safer for professional and technical personnel than those previously reported (53). Without direct handling at any time, the suitably diluted radiogold suspension is introduced into the patient by the hydrostatic pressure of a siphon system (Fig. 143). The hazard of blowouts is obviated by eliminating syringe

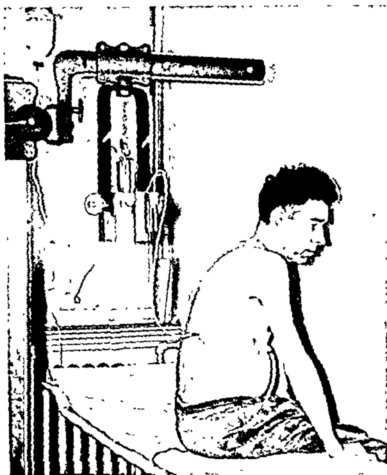


Fig 143 Intrapleural Therapy with Au^{198}

Apparatus for intrapleural administration of radiogold colloid in our laboratory by means of hydrostatic pressure of a siphon system Note massive lead chamber shielding container holding Au^{198} Personnel remain at a distance from the patient during treatment, for protection from penetrating gamma radiation Compare with Fig 144

pressure to force fluids through the system. The entire administrative procedure usually takes about three minutes, with most of the radioactive material passing into the patient in about half a minute. With this method, radiation from the patient himself after treatment presents the only potential hazard. According to the regulations of the United States Atomic Energy Commission, any patient whose body contains more than 30 millicuries must be hospitalized. When he has received 100 millicuries, he should be at least six feet from other patients and the nurse may be allowed to work within two feet of such an individual for a maximum of 20 minutes a day. This time may be doubled after three days because of the physical decay of the radioisotope.

COMPLICATIONS

Patients may present evidence of a distinct pleuritis with a pleural friction rub and some pleural and diaphragmatic pain. Systemic radiation effects (nausea and vomiting) are uncommon even after single dc of 150 millicuries. Moderate and transitory impairment of blood e ments has been observed, but rarely constitutes an obstacle to furth treatment. Accidental release of radiogold into the subcutaneous tissuc of the chest has occurred without slough or other untoward complica tions (37).

LIMITATIONS OF RADIOGOLD

Experience indicates that the radiogold colloid is a useful but far from ideal therapeutic tool in the management of malignant pleural effusion. It is expensive to employ, deteriorates rapidly, emits a hazardous gamma radiation, produces only minimal radiation changes on the surface of the tumor and pleura, fails to flocculate consistently, rapidly, or homogeneously on the serous membrane, and does not control the effusion in about 50 per cent of the cases. Bone marrow depletion, while very uncommon, can be severe. Four such cases were reported by Botsford et al (6).

EXPERIENCES WITH COLLOIDAL $CrP^{32}O_4$

These limitations of Au^{198} stimulated our interest in 1953 in a radioisotope with a purely beta emission, greater ionization per microcurie, longer half-life, and ability to flocculate rapidly on the pleura. These criteria appeared to be satisfied by a colloidal suspension of radiophosphorus ($CrP^{32}O_4$), with a half-life of 14.3 days, energetic beta particle of 0.7 Mev average energy, penetrating to a maximum of 8 mm in tissue, and greater ionization per disintegration. The absence of a gamma ray component provides greater safety, and convenience and economy in

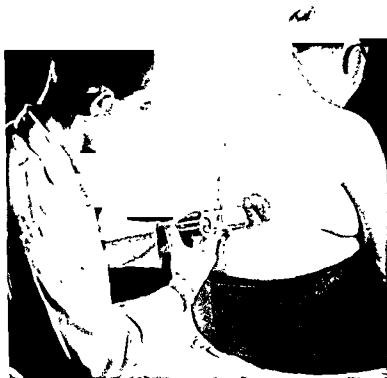


Fig 144 *Intrapleural Therapy with P^{32}*

Technique for intrapleural use of radioactive colloidal chromic phosphate ($CrP^{32}O_4$) in our laboratory Note the use of a conventional 10-cc glass syringe, shielded by a 10-mm plastic cylinder Complete protection against the pure beta radiation is thus provided with relative ease and safety of administration The absence of a gamma ray component spares patient and personnel the hazards of systemic radiation

preparing, shipping, handling, administration, and in the management of the patient after treatment.

The distribution of this agent after intrapleural injection and its usefulness was experimentally studied in our laboratory in 12 human subjects with malignant pleural effusion, principally of bronchogenic origin (45). After removal of most of the fluid, 10–20 millicuries of $CrP^{32}O_4$ were injected. Insignificant levels of radioactivity were found in the blood, urine, spleen, liver, and bone marrow. Similar findings in distribution studies have been reported in detail by Root, *et al.* (41) and McCormack and his colleagues (35). In all of our patients there was a remarkably prompt decrease of radioactivity in the pleural fluid within several minutes after the injection, and almost complete flocculation on the pleural membrane in less than 24 hours. It is of particular interest that isolation of the patient and special ward precautions for radiological safety of hospital personnel were not required.

There were no untoward reactions, local or systemic, nor was there any impairment of the blood elements. Our preliminary clinical results suggest that the benefits from P^{32} may prove to be comparable to those obtained with Au^{198} without the limitations of the latter. Jaffe has independently reported good results with this agent in 20 out of 30 patients with carcinomatous pleural effusion (24). It is obvious that more extended clinical experience will be required before final evaluation can be made.

Radioactive colloidal yttrium (Ytt^{90}) with a pure beta emission of high energy (2.18 Mev) and short half-life (2.51 days) is under investigation in several clinics for intrapleural as well as interstitial application, but a clinical appraisal has not yet become available.

INTERSTITIAL THERAPY

In approximately 50 per cent of the explored cases of bronchial cancer, the surgeon is confronted with a non-resectable primary lesion or fixed regional lymph nodes. In such cases, important palliative benefits and occasional prolongation of useful life may be gained through intensive postoperative roentgen therapy. The possibility of improving these benefits through the interstitial administration of nuclear radiation at the time of surgery has not yet been adequately explored. In this manner a high degree of selective beta radiation could be introduced into tumor masses with less likelihood of trauma to adjacent normal structures. Radon seeds have long been available for implantation but they present technical difficulties as well as radiation hazards and have not often been utilized by thoracic surgeons in an effort to retard the malignant growth.

In recent years, a variety of artificially made radioactive materials in the form of seeds, grains, and wire and colloidal suspensions have become available for this function

RADIOACTIVE COLLOIDAL GOLD (Au^{198})

It has now become feasible to infiltrate an accessible neoplasm with a colloidal suspension of radioactive material as a helpful adjunct to surgical or roentgen ray therapy Radioactive colloidal gold has been utilized for this purpose with some measure of success in advanced carcinoma of the prostate (28, 29) and in carcinoma of the female pelvis (48). It may well be applied by the thoracic surgeon, in collaboration with the radiologist, at the time of surgery for cancer of the lung, should the primary lesion or regional nodes be regarded as non-resectable. Taplitz has in fact designed a remote-control precision injector for interstitial or intracavitary injection of Au^{198}—for use in the operating room (50). The principal limiting factor in the use of a colloidal suspension for direct infiltration lies in the inability of friable tissue to contain the fluid which acts as a vehicle for the radioactive colloid A further difficulty is that of adequate distribution in very large tumor masses Kerr and his colleagues, for example, in treating prostatic cancer, have found it possible to sterilize completely only small tumor masses by radiogold alone (29) This lesion, however, is notably and consistently radioresistant. The greater vulnerability of bronchial cancer may provide a more fertile field for this form of adjunct ionizing radiation

EXPERIENCE WITH COLLOIDAL $CrP^{32}O_4$

A colloidal suspension of radioactive colloidal chromic phosphate ($CrP^{32}O_4$) was first utilized for interstitial irradiation of cancer in experimental animals by Allen, Hempelmann, and Womack (1) Clinical investigation of this radiocolloid for interstitial use in our patients was initiated in 1952 (45) The destructive action of P^{32} beta emission in a volume of tumor tissue is fifty times that of an equal quantity of Au^{198}. The absence of gamma radiation makes it possible to handle $CrP^{32}O_4$ in an ordinary glass syringe shielded by a cylinder of lucite 10 mm. in thickness This is in sharp contrast to the heavy lead shielding which makes for awkward and unwieldy handling of syringes containing radiogold. In 24 patients with metastatic lesions from a variety of primary sites, including bronchogenic carcinoma, this agent proved to be an effective interstitial source of ionizing radiation Distribution studies revealed insignificant levels of radioactivity in the blood, urine, spleen, liver and bone marrow It is of interest that Jaffe has recently described tumor regression in 18 of 28 patients with prostatic cancer receiving interstitial

injections of $CrP^{32}O_4$ (24). A three-year arrest of a malignant mixed tumor of the tongue has been reported by Mumma (39).

The limitations of radioactive colloidal chromic phosphate are the same as those of other radiocolloids intended for interstitial cancer therapy, *i.e.*, the tumor surface must be intact, homogeneity of distribution is difficult of attainment, and the optimal dose (in microcuries per gram) has not been well established.

Radioactive Gold Seeds

Some of the limitations of fluid agents for interstitial therapy may be overcome through the more precise *implantation of radioactive gold* seeds, supplying multiple tiny intensive sources of gamma rays (20, 40). The beta particles are shielded out by means of inactive gold sheathing or tubing. Seeds of the required number and strength may be instantly cut to order in the operating room from previously irradiated gold wire.

Despite these advantages of radiogold seeds, their manual implantation involves the same mechanical and protection difficulties encountered in the use of radon seeds. A precision instrument in the form of a gun has therefore been developed for the speedy, safe, and accurate implantation of multiple small sources of radiation in the form of platinum-covered gold grains (23). This instrument is of particular value for the type of volume implant that is most likely to be required in non-resectable bronchial cancer. It is always available to the surgeon at the time of exploratory operation.

Other Interstitial Agents

A number of interesting investigations are in progress, involving the interstitial application of other radioisotopes such as palladium^{109} (half-life 13.1 hours, beta energy 0.95 Mev), tantalum^{182} (half-life 117 days, beta 0.5 Mev, gamma 1.1 Mev), yttrium^{90} (half-life 2.54 days, beta energy 2.18 Mev), and cobalt^{60} (half-life 5.3 years, gamma 1.17, 1.33 Mev), in the form of grains, colloids, needles, wire, beads, and seeds. The early results of clinical trials will be awaited with interest.

ENDOBRONCHIAL THERAPY

Experimental methods have been developed for delivering intensive radiation via the *transbronchial* route to specific lung segments and to regional lymph nodes as well, using radioactive isotopes. Meneely, Hahn, and their colleagues (16, 17, 19, 36) demonstrated that when a colloidal suspension of radiogold (Au^{198}) was introduced in this manner, the *fluid* was rapidly absorbed, leaving the inert radioactive material uniformly distributed in the lung alveoli for a considerable number of days, and

delivering intensive ionizing radiation. Another radioisotope of gold of much higher activity (Au^{199}) has been proposed for this function. Theoretically, a single lobe harboring a neoplasm could thus be selectively and aggressively irradiated should the lumen of the appropriate bronchus remain patent. Since a patent bronchus is an uncommon finding in this disease, the obstructing tumor would need to be surgically fulgurated or reduced in size by well-directed external x-radiation. At best, after successful alveolar deposition, only the periphery of the tumor would receive adequate irradiation from the shallow tissue-penetration of the beta rays of Au^{198}.

The regional lymph nodes receive only a trivial amount of irradiation in this procedure because the gold colloid takes from 10 to 15 days to reach them and is no longer effective. This limitation might be overcome by employing a more energetic beta emitter of much longer half-life such as P^{32} in colloidal chromic phosphate. However, Hahn and his group (16, 17) chose to exploit the physiology of pulmonary lymphatics. When these investigators deposited *silver-coated* radiogold into the bronchus, this material was rapidly transported via the lymphatics to the regional lymph nodes. These nodes received remarkably high radiation dosage, completely obliterating their architecture. Even the contralateral lymph nodes concentrated radioactivity with great frequency, providing eloquent evidence of the lymphatic cross-drainage frequently associated with primary cancer of the lung and breast. Only negligible quantities found access to the blood stream.

Hahn suggests that radioactive colloidal silver^{111} (half-life 7.5 days, 1.06 Mev beta ray energy) be employed in a similar manner in operable patients supected of early nodal involvement, to be followed in ten days to two weeks by pneumonectomy (19). It is hypothecated that collateral lymphatic drainage would take over in situations where metastatic tumor blocked the regular lymphatic channels. However, one could hardly expect adequate interstitial irradiation by this method, were the lymph nodes to be grossly involved by malignant disease.

Still another method for specific irradiation of regional lymph nodes has been introduced by Bryant, Berg, and Christophersen (7). Colloidal radiogold was directly injected into the bronchial submucosa of dogs by means of a long needle introduced through a bronchoscope. The colloid was carried through the lymph channels to the recipient nodes in high concentration by means of phagocytic activity. Here again, in nodes almost completely replaced by tumor, it appears quite unlikely that Au^{198} would be helpful.

Contact irradiation of carcinoma of the major bronchi by means of radiocobalt (Co^{60}) beads or pearls has been recently described by Fischer (9). An applicator consisting of several tiny beads strung on a wire is

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introduced with care into the infiltrated bronchus under fluoroscopic control, and left in place for several hours (during general anesthesia). Cobalt[60] (half-life 5.3 years) emits penetrating gamma rays of 1.17 Mev and 1.33 Mev, simulating a radium source. Such a procedure may have limited application, but would probably serve well as an adjunct to external radiation therapy.

INTRAVENOUS THERAPY

The possibility of localizing a radioactive colloidal substance within a specific lung segment via the *intravascular* route has been seriously considered However, the small gold particles presently available (20–200 mμ) would pass through the lung capillaries to lodge in the liver, spleen, and bone marrow The successful vascular localization of a radioactive isotope within a segment of the human lung was first reported by Muller and Rossier (38) in 1951, utilizing radiozinc (Zn^{65}) in the form of a non-soluble dispersoid sulphide. By means of a diffuse microembolism, radiozinc particles became completely fixed within the lung segment, producing an intensive irradiation which was apparently well tolerated

Muller and Rossier describe a patient who received several hundred millicuries of radiozinc and died with generalized metastases eight months after the treatment. Only a small fibrous rest remained of a very large primary tumor (squamous cell type). Using charcoal powder as a carrier substance, the authors prepared large radiogold particles (30–50 μ in diameter) and injected these into the lungs of four other patients by cardiac catheterization. The catheter was directed into a main pulmonary artery or a branch of it. In one reported case, intensive and combined pulmonary and pleural radiation with radiogold was employed, followed by real improvement in the patient's condition Total atelectasis of the right lung was cleared through destruction of an invasive tumor in the main bronchus. The introduction of these and similar radiomaterials into branches of the pulmonary or bronchial arteries during thoracic surgery remains to be undertaken in patients operated upon and found to have a non-resectable lesion.

TELECURIE THERAPY

At present, the only hope for prolongation of useful and comfortable life in patients with non-resectable lung cancer lies in delivering intensive radiotherapy to a selected group of such individuals with limited intrathoracic disease. Conventional therapy (200–260 Kev), under optimal conditions, can perform this task well In our opinion, however, the most important advance in our ability to administer such radical treat-

ment—approaching cancerocidal dose levels—has been the utilization of high energy radiation, in the range of 1–3 Mev Such radiation has greater "reaching power" for deep-seated lesions, excites only mild skin reactions, and induces minimal systemic discomfort. Our own experience with this modality has convinced us that the palliative benefits of roentgen therapy may thus be appreciably enhanced A more complete discussion may be found in the chapter on radiotherapy.

Cobalt^{60}, produced in the nuclear reactor, provides an economic substitute for a 1–2 million volt x-ray generator, and is rapidly becoming more widely available (4) Early clinical reports emphasize the ease and facility with which relief can be provided in the majority of patients so treated (11) Mounted in a revolving head, cobalt^{60} affords the additional advantages of rotation therapy with the patient in the reclining position Its principal disadvantages include relatively low output of present sources and large penumbra These are of a temporal nature and will be largely overcome as soon as cobalt^{60} sources of much greater specific activity and smaller focal size become generally accessible.

Other promising sources of high energy nuclear radiation include iridium^{192}, now utilized in England (10), and cesium^{137} (half-life 37 years, energy 0 69 Mev), now under investigation by the United States Atomic Energy Commission

FUTURE PROSPECTS

While the role of the radioisotopes in the adjunct management of the intrathoracic lesion appears versatile and promising, these agents all have the same outstanding shortcoming—inability to cope with widely generalized cancer Sooner or later—generally within less than two years—nine out of every ten patients will develop inaccessible remote metastases This is the heart of the problem As yet, there appears to be no immediate prospect of specific localization of intensive nuclear radiation in

providing a "carrier" substance to bring annihilating radiation to remote tumor foci

In the meantime, there is a rapidly mounting number of such patients (25,000 in 1954 in this country alone) who demand our best efforts for the control of their distress and disability, and for possible prolongation of useful life Optimal combinations of nuclear radiation and roentgen therapy, surgery, and chemotherapy, must soon be found to afford maximum palliative benefit for such individuals (33, 34, 44).

It is earnestly to be hoped that our colleagues in the biological and physical sciences will be inspired to provide, through fundamental investigation, a fresh and more effective therapeutic approach in this disheartening field where so much help is needed by so many.

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15

Chemotherapy of Lung Cancer *

DAVID A. KARNOFSKY

Only a few chemotherapeutic procedures of limited value are presently available for the treatment of lung cancer. This is a source of great disappointment, since the inadequacies of surgery and radiation therapy, even when applied in an optimal manner, are all too apparent. Hope is ever present that chemicals will be found capable of destroying, restraining, or controlling the growth of lung cancer, wherever it may exist in the body, without causing undue injury to the normal tissues of the host. While the means of achieving this objective are not immediately foreseeable, the urgencies of the disease and the insistence of the public have stimulated numerous and varied attacks on lung cancer. It seems proper to review briefly some aspects of the problems concerned with the chemotherapy of lung cancer before describing the chemotherapeutic procedures useful in man.

THEORETICAL AND LABORATORY ASPECTS

A basic objective in cancer research is to discover distinctive qualitative biochemical differences between normal and neoplastic cells. This achievement could result in a direct and logical search for chemotherapeutic agents. While such fundamental studies are being intensively pursued there is little, if any, knowledge of a primary biochemical derangement common to all cancer cells.

In a more specific but limited manner, it has been possible to damage some types of cancer cells because they retain certain special properties from their normal tissues of origin, which render these cells susceptible to chemical changes in their environment. If the distinctive properties of a particular type of cancer have no connection with any organ or tissue

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essential for life, the growth of the normal tissue and its neoplastic analogue can be inhibited without jeopardizing the survival of the host. This therapeutic situation has been achieved successfully in several types [illegible]

functional thyroid cancers, in which radioactive iodine is concentrated in the cancer as well as in the normal thyroid gland, with resultant severe damage to both structures.

If the biochemical properties of the neoplastic cell that render it vulnerable to certain drugs are similar to those present in vital normal tissues, the therapeutic situation is far more difficult, a satisfactory but partial result will depend on some quantitative difference between the susceptibility of the normal and cancer cells This mechanism apparently operates, for example, in some patients with acute leukemia, in whom the requirement of the leukemic cells for folic acid compounds appears to be much higher than that of the normal blood-forming tissues, so that the administration of the folic acid antagonists (methotrexate®) may temporarily eliminate the great majority of leukemic cells without interfering with normal hematopoiesis. It also operates in chronic lymphatic leukemia, where the leukemic cells may be extremely vulnerable to triethylene melamine (TEM), so that the leukemic process is almost obliterated, with actual improvement in normal blood cell formation

In planning a chemotherapeutic attack on lung cancer, it would be desirable, at the outset, to be able to demonstrate some characteristic biologic property of this form of cancer While the state of our knowledge concerning lung cancer is presented in detail elsewhere in this volume, some opinions as to its morphology, biochemical abnormalities, growth characteristics, functional properties, and blood supply may be broadly summarized here

Morphology Carcinoma of the lung arises from the bronchi or bronchioles More than 80 per cent of lung cancers are classified as epidermoid carcinoma of the oat cell, anaplastic, or squamous cell varieties (15). These tumors, as far as we know, have no characteristics distinguishing them from other epidermoid carcinomas of the upper respiratory tract, mouth, or esophagus Terminal bronchiolar carcinoma may possibly fall into a different category.

Biochemical abnormalities There are few if any data in man indicating that bronchogenic carcinoma has distinctive biochemical properties

Growth characteristics Lung cancers have survived better than most other human tumors when explanted to the chorioallantoic membrane of the chick embryo (13) (Fig 145), although these tumors could not be



Fig 145 Histologic appearance of human lung cancer explanted to the chorioallantoic membrane of the chick embryo

A Biopsy, supraclavicular node.

B Section of tumor ten days after explantation to the chorioallantoic membrane Note the mitotic figure The tumor was explanted in the eight-day embryo

C Higher magnification of a tripolar mitosis in a tumor cell surviving on the chorioallantoic membrane

This tumor did not grow on subsequent transfer in the chick embryo

maintained by continuous transfer from egg to egg. Toolan (25) has found that human lung cancer will grow in many instances when transplanted to the cortisone-treated rat and hamster Such a high degree of autonomy on heterologous transplantation suggests that most bronchogenic carcinomas do not have any special growth requirements or dependencies on host factors. The development of transplantable human lung cancers in animals may facilitate the laboratory trial of chemotherapeutic agents against this form of cancer

Functional properties There is no evidence that bronchogenic carcinoma has any special functions, concentrates particular substances, manufactures special secretions, or has any unusual requirements for chemical precursors for cell growth and multiplication Since lung cancer is more common in males, some relation to sex hormones has been suggested, but while sex hormones may have some role in its origin, alteration in the environment of the established cancer, by castration or estrogen therapy, has been of no clinical benefit

Blood supply. Tumors require, of course, a blood supply for growth It has been possible to deliver a high concentration of some drugs such as nitrogen mustard, to the tumor-bearing area by intra-arterial injection (1, 14). On this basis, it has been suggested that injecting a chemical into the pulmonary artery to the lobe containing the cancer will expose it to a high concentration of the agent (18) Several studies (7, 27) have demonstrated, however, that primary bronchogenic carcinoma derives its blood supply from the bronchial arteries, which arise from the descending aorta As the tumor grows these vessels enlarge to accommodate it The bronchial artery drains in large part into the pulmonary veins It is probable, therefore, that chemicals injected into the brachial vein, or a pulmonary artery, will traverse the aerated portion of the lung, and then drain into the pulmonary veins without coming into direct contact with the tumor The tumor would subsequently receive through the bronchial artery the same concentration of the drug as the other tissues of the body. In order to achieve a higher concentration of the drug in the tumor, it would be necessary to inject the appropriate bronchial artery, a much more difficult technical procedure It may be possible to modify the blood supply to the tumor so that an effective agent could be delivered directly to the tumor in high concentrations (24)

A number of other general studies on cancer chemotherapy may find some direct application to the treatment of lung cancer. One approach is the study of cancer cells for specific antigens which may be used to stimulate antibody production (20) Tumor suspensions have been injected into rabbits, and the resultant antibodies purified to obtain the maximum concentration of tumor-localizing antibodies These anti-

bodies are also tagged with radioactive isotopes, so that the tumor cells may be irradiated by the specifically localized antibodies.

Certain viruses have been shown to cause necrosis in transplantable tumors (17). Studies are in progress to discover other types of tumor-necrotizing viruses, or to isolate mutant strains of oncolytic viruses which can selectively destroy cancer cells in general, or some forms of cancer.

Extensive empirical laboratory screening programs are endeavoring to discover more effective chemotherapeutic agents. A great number of chemicals and biological substances are being tested for their chemotherapeutic activity, as measured by their ability to inhibit the growth of tumors in animals, and by other procedures (5, 23). Substances exhibiting some degree of activity in these laboratory tests, after careful toxicity studies, are then evaluated for therapeutic activity against various forms of neoplastic disease in man (9). The clinical trials of each candidate therapeutic agent usually include several patients with far-advanced lung cancer.

PRACTICAL RESULTS

Despite the intensive and wide-ranging laboratory and clinical efforts, few advances have been made in the management and control of non-resectable or recurrent lung cancer. Radiation therapy in one of several forms, is the most effective palliative measure available, and among the chemicals, the polyfunctional alkylating agents (nitrogen mustard, triethylene melamine, and related compounds) are the only ones with some degree of oncolytic activity. The adrenal cortical hormones may be of supportive value in some cases.

Nitrogen Mustard

The most useful chemical, in our experience, is methyl-bis(β-chloroethyl) amine hydrochloride (HN_2) Mustargen®. Mustargen® is available in vials containing 10 mg. of the powder. It is readily soluble in water, and the solution is prepared shortly before injection. Our usual procedure is to start an intravenous infusion of physiological saline, and after the solution is running freely into the vein, Mustargen® is injected, usually within one minute, into the tubing. In patients with a superior vena cava compression syndrome, the increased venous pressure may cause stasis of the injected drug in the veins, with resultant thrombosis of the superficial veins. In these cases, therefore, the arm should be elevated during injection. Venous thromboses are usually avoided but if the drug extravasates, a severe and prolonged local reaction with pain, induration, and fibrosis, and occasionally a local slough, may occur.

The usual course of Mustargen® is a total dose of 0.4 mg./kg. of body weight (25–30 mg. in the average adult). In the past this total dose has

been fractionated in four daily doses of 0.1 mg./kg., but more recently we have given the entire course (0.4 mg./kg.) in a single injection. The nausea and vomiting following the large dose is no more severe than after each fractionated dose, the therapeutic response occurs more rapidly, and the patient is spared a protracted course of treatment. The large dose is only indicated, however, if the patient shows no evidence of impaired hematopoiesis.

Nausea and vomiting usually, but not always, follow the injection of Mustargen®, occurring within one-half to two hours following a dose of 0.4 mg./kg. and several hours after the fractionated dose. This reaction may be diminished by injecting 0.250 gm. sodium amytal or 0.120 gm. sodium luminal intramuscularly shortly after the Mustargen® injection, and the sedative is repeated in two hours if vomiting is severe. Thorazine®, 0.025 gm. intramuscularly, may be given on the same schedule. Mustargen® is often given late in the afternoon or evening and the patient sedated during the night; by the next morning the patient has usually recovered from the nausea and vomiting.

The most serious toxic effect of Mustargen® is damage to the bone marrow. While the drug acts on the hematopoietic cells within a few minutes after injection, the evidences of bone marrow depression slowly evolve in the peripheral blood, and the maximal effects usually occur two to three weeks after injection. At the recommended dosage a moderate leucopenia and thrombocytopenia develop, and recovery is rapid, whereas excessive doses will cause severe leucopenia, thrombocytopenia with petechiae and other bleeding manifestations, and anemia, a syndrome which can be fatal. Bone marrow depression is thus the limiting factor in dosage. The recommended dosage of 0.4 mg./kg. has been well tolerated in patients with lung cancer and larger doses have been given in some clinics (2, 4). It is preferable, however, to wait two to four weeks after a course of Mustargen®, and if the peripheral blood count is not appreciably depressed, and if clinically indicated, another course of Mustargen® may then be given.

Mustargen® acts systemically and its adverse effects are seen principally on cells which are undergoing rapid multiplication, as well as on the constituents of the lymphatic and hematopoietic tissues. Its therapeutic action in lung cancer may, therefore, be twofold: 1) to temporarily damage or inhibit the growth of the lung cancer cells, and 2) to diminish the inflammatory reaction around the tumor and in the local lymph nodes. A slight, and often objectively measurable, reduction of the bulk of the tumor and the inflammatory reaction in the complex and strategic areas of the thorax often results in marked symptomatic improvement. The usual therapeutic effect lasts from two to eight weeks, and subse-

quent courses of Mustargen®, while sometimes beneficial, are usuall progressively less effective (10). On the basis of these effects of nitrogen mustard certain indications for its use are suggested.

Superior vena cava syndrome. In the patients with superior vena cava compression syndrome, Mustargen® produces rapid relief of swelling and decrease in symptoms in more than 80 per cent of the cases (3, 10, 21). This response may occur within 24 to 48 hours and is associated with objective evidence of regression in enlarged nodes and in decreased widening of the mediastinum (Fig 146). Since this response rarely persists for more than two to eight weeks, it is usually desirable to follow Mustargen® by local x-ray therapy. Mustargen® preceding x-ray therapy in these patients may have several advantages, it produces more rapid relief of symptoms and it does not cause edema in the tumor, a distressing reaction which may follow the initiation of x-ray therapy in conventional dosage. By pre-treating with Mustargen®, x-ray therapy may then be given more rapidly, 3000 r tumor dose has been delivered to the mediastinum in eight treatments without unduly severe reactions (12) Also, the leucopenia produced by nitrogen mustard is not aggravated by local irradiation, even at high doses.

Disseminated cancer. In patients with disseminated lung cancer, particularly anaplastic carcinoma, Mustargen® may induce tumor regression temporarily in distant areas, such as the liver, brain, and skin It h caused prompt neurologic improvement in patients with cerebral meta tases This result can then be enhanced and prolonged by x-ray to th brain. Similar results have been seen in patients with liver involvement (19)

When x-ray therapy is not feasible Mustargen® has been used to relieve symptoms from non-resectable lung cancer, where x-ray therapy is not available If the patient responds to the initial course of treatment, further doses of the drug at four- to six-week intervals may be indicated if the blood picture permits. Also, in patients who have relapsed after a definitive course of x-ray therapy, Mustargen® may sometimes give temporary relief.

It is recommended that Mustargen® be reserved for the treatment of symptoms since there is no evidence that the early use of Mustargen® delays the progression of the disease The nature and degree of symptomatic relief afforded by nitrogen mustard is summarized in Tables XI and XII

Intrapleural Mustargen®. Mustargen® has been given intrapleurally for recurrent pleural effusion A thoracentesis is performed, and most of the pleural fluid is removed A solution of Mustargen®, 1 mg/cc., is then injected directly into the pleural space The usual dose is 0.4 mg/kg; this dose is selected because the drug, even if completely absorbed sys-

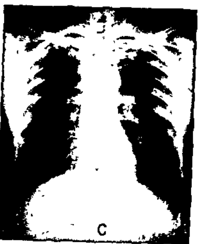






Fig 146 A 44-year-old man with bronchogenic oat-cell carcinoma was admitted with signs of a superior vena caval syndrome A, film taken January 21, 1952, showed a middle superior mediastinal mass The patient received 6 mg of TEM intravenously on January 20 and January 21, *and, since he was not improved, on January 23 he received 0 3 mg/kg HN_2 There was prompt symptomatic relief* B film taken January 30, 1952, showed regression of mediastinal mass A tumor dose of 3000 r was given to the mediastinum C film taken February 13, 1952, showed further improvement The patient had a ten month remission *Manifestations of the disease due to generalized metastases occurred in* November 1952, and *the patient* died April 2, 1953, with evidence of severe liver insufficiency due to metastatic disease (from Am J *Surg*, 89 526–537, 1955)

TABLE XI

IMMEDIATE RELIEF IN SOME SYMPTOMS AS A RESULT OF MUSTARGEN® THERAPY (10)

Symptom	No Patients with Symptom	% of Improvement			
		Relief	Partial Relief	No Relief	Worse
Cough	28	21	47	32	0
Hemoptysis	14	21	43	36	0
Dyspnea	28	21	43	36	0
Weakness	32	13	44	43	6
Pain	26	31	34	35	0
Compression of superior vena cava	9	67	22	11	0

TABLE XII

PER CENT OF PATIENTS SHOWING OBJECTIVE AND SUBJECTIVE IMPROVEMENT FOLLOWING MUSTARGEN® THERAPY (10)

Group	No Cases	Subjective			Objective		
		G	F	0	++	+	0
Anaplastic	7	43	28	29	28	29	43
Epidermoid	10	30	50	20	30	10	60
Total group	21	28	43	29	24	14	62

Abbreviations have the following meaning

G—good
F—fair
0—none

++ Marked regression
+ Definite regression

temically in active form, will not exceed the amount tolerated by the intravenous route The patient is moved around following the injection so that the drug will come into contact with the pleural surfaces In some cases a pleural reaction with an obliterative pleuritis apparently results The systemic effect of intrapleural Mustargen® is similar to that following its intravenous administration. Nausea and vomiting commonly occur Although ordinarily the bone marrow depression is not

severe, some patients seem to absorb the drug completely, as suggested by the definite leucopenia which appears Intrapleural Mustargen® is probably of some clinical value in less than 25 per cent of the patients with recurrent pleural effusion from lung cancer, its merit as compared to radioactive gold has not been determined

Triethylene Melamine (TEM) TEM is similar to nitrogen mustard in its therapeutic effects, and it can be given orally (6, 11, 22) It is available in 5-mg scored tablets The usual procedure is to take each dose about one hour before breakfast on an empty stomach It is taken with plain water, since TEM is highly reactive with organic materials In some clinics it is given with 2 gm sodium bicarbonate, because it is not reactive in an alkaline environment (11) Absorption of oral TEM is variable, and dosage must be carefully controlled As with nitrogen mustard, excessive dosages will produce a delayed and severe bone marrow depression

The usual dose schedule is 5 mg TEM for two days, and then the patient is seen at weekly intervals and a blood count taken If the leucocyte count is unchanged and the patient is not improved, further TEM, in 5 to 10 mg weekly doses, is given The usual total dose tolerated in the first month during a course of treatment ranges from 20 to 40 mg, but some patients have required much larger doses The clinical response to oral TEM usually occurs slowly over a period of two to four weeks, and is, therefore, rarely as striking as that following intravenous Mustargen® (11) TEM can be given as maintenance therapy if a favorable response occurs In general, we prefer the use of intravenous nitrogen mustard The entire course of treatment may be given in a single injection, and improvement, if it occurs, is prompt

There are a number of other polyfunctional alkylating agents, including triethylene phosphoramide, thiotriethylene phosphoramide, and p-(N,N-di-2-chloroethyl)amino phenylbutyric acid (CB1348) There is no evidence that they are therapeutically superior to Mustargen® or TEM

ADRENAL CORTICAL STEROIDS

Cortisone, hydrocortisone, and related steroids do not appear to have any specific effect on lung cancer Their use in certain situations is justified a) in patients receiving intensive x-ray therapy to the lung, cortisone has been given during or following x-ray therapy to reduce the inflammatory reaction in the pulmonary bed, b) adrenal metastases are frequent in lung cancer, and in some cases adrenal cortical insufficiency may be present, although difficult to diagnose—cortisone will correct this difficulty, c) in patients with far-advanced disease, cortisone may exert a

nonspecific supportive effect. The dosage of cortisone is usually in the range of 100 mg./day but if this is not effective, larger doses have been given. Higher dosage, of course, may induce physiological disturbances and increase the susceptibility to infection.

COMBINATION AND PROTECTION STUDIES

The use of nitrogen mustard in combination with x-ray therapy has already been discussed. Besides the clinical advantages, nitrogen mustard and x-rays have some additive effects as far as damage to the tumor cells is concerned, although there is no evidence that this combination has prolonged life. Mitchell (16) has used Synkayvite, a synthetic vitamin K, to sensitize the tumor cells to the action of x-rays. In a series of 47 cases he obtained an average prolongation of four to five months in survival over patients receiving x-ray therapy alone. While he concluded that the use of Synkayvite produced a small but useful prolongation of life, the evidence is not convincing.

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Other chemotherapeutic agents. A number of other agents have been tested against lung cancer, including the folic acid antagonists, diaminodichlorophenylpyrimidine, 6-mercaptopurine, and azaserine, but there is no evidence that they exerted a favorable effect on the disease.

CANCER METASTATIC TO THE LUNG

It is important to establish the site of origin of non-resectable cancer in the lung before initiating therapy. For primary lung cancer and metastatic epidermoid and adenocarcinomas from most sites, the treatments available, and their limitations, have been described. Some types of metastatic carcinoma, including those originating in the prostate, breast, and thyroid, may respond to specific measures, and there are several drugs which occasionally exert favorable effects on the lymphomas and leukemias. It is emphasized, however, that in most instances x-rays are the most satisfactory form of treatment. The available chemotherapeutic agents are summarized in Table XIII. For details, see chapter on secondary cancers of the lung.

TABLE XIII

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Chronic myeloid	Myleran, urethane, TEM, 6-mercaptopurine, Fowler's solution
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SUMMARY

X-ray therapy is the major method of palliation in non-resectable primary or recurrent lung cancer Nitrogen mustard, TEM, and related compounds, and the adrenocortical hormones, may be of benefit, but the response is usually brief and there is no assurance that treatment appreciably prolongs life It is essential to progress, however, that we intensify our attack on this disease and study all possible methods that may contribute to its control From the patient's point of view, in most instances it is desirable to maintain an aggressive therapeutic approach, and to use the available methods as effectively as possible to relieve discomfort and to sustain morale

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It is important to establish the site of origin of non-resectable cancer in the lung before initiating therapy. For primary lung cancer and metastatic epidermoid and adenocarcinomas from most sites, the treatments available, and their limitations, have been described. Some types of metastatic carcinoma, including those originating in the prostate, breast, and thyroid, may respond to specific measures, and there are several drugs which occasionally exert favorable effects on the lymphomas and leukemias. It is emphasized, however, that in most instances x-rays are the most satisfactory form of treatment. The available chemotherapeutic agents are summarized in Table XIII. For details, see chapter on secondary cancers of the lung.

TABLE XIII

CHEMOTHERAPEUTIC PROCEDURES USED IN METASTATIC AND LYMPHOMATOUS INVOLVEMENT OF THE LUNG (8, 12)

Diagnosis	*Specific Chemotherapeutic Measures*
Carcinoma of breast	Estrogens, androgens, adrenal steroids and surgical ablative procedures (ovariectomy, adrenalectomy, hypophysectomy)
Carcinoma of prostate	Estrogens and/or castration
Carcinoma of thyroid	Radioactive iodine
Lymphoma	Nitrogen mustard, TEM, and related compounds, adrenal steroids
Leukemia	
Chronic myeloid	Myleran, urethane, TEM, 6 mercaptopurine, Fowler's solution
Chronic lymphatic	TEM, adrenal steroids
Acute	Amethopterin, 6-mercaptopurine, adrenal steroids

SUMMARY

X-ray therapy is the major method of palliation in non-resectable primary or recurrent lung cancer Nitrogen mustard, TEM, and related compounds, and the adrenocortical hormones, may be of benefit, but the response is usually brief and there is no assurance that treatment appreciably prolongs life It is essential to progress, however, that we intensify our attack on this disease and study all possible methods that may contribute to its control From the patient's point of view, in most instances it is desirable to maintain an aggressive therapeutic approach, and to use the available methods as effectively as possible to relieve discomfort and to sustain morale

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nonspecific supportive effect The dosage of cortisone is usually in the range of 100 mg/day but if this is not effective, larger doses have been given. Higher dosage, of course, may induce physiological disturbances and increase the susceptibility to infection.

COMBINATION AND PROTECTION STUDIES

The use of nitrogen mustard in combination with x-ray therapy has already been discussed Besides the clinical advantages, nitrogen mustard and x-rays have some additive effects as far as damage to the tumor cells is concerned, although there is no evidence that this combination has prolonged life. Mitchell (16) has used Synkayvite, a synthetic vitamin K, to sensitize the tumor cells to the action of x-rays In a series of 47 cases he obtained an average prolongation of four to five months in survival over patients receiving x-ray therapy alone While he concluded that the use of Synkayvite produced a small but useful prolongation of life, the evidence is not convincing.

Weisberger, *et al.* (26) has shown that L-cysteine protects animals against the bone marrow depressant activity of Mustargen®. They suggested that the use of L-cysteine in man would protect the bone marrow against the toxic effects of nitrogen mustard without diminishing the effect of the drug on the lung cancer. This is actually no satisfactory evidence for a selective protective action of cysteine on the bone marrow, and it seems likely that cysteine will diminish the toxicity of nitrogen mustard for both the bone marrow and the tumor.

Other chemotherapeutic agents A number of other agents have been tested against lung cancer, including the folic acid antagonists, diamino dichlorophenylpyrimidine, 6-mercaptopurine, and azaserine, but there is no evidence that they exerted a favorable effect on the disease.

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16

Medical Management of the Surgically Incurable Patient

EDGAR MAYER AND JOHN LADUE

The fact that 90 per cent or more of the patients with lung cancer are at present surgically incurable, and that their total number is steadily increasing, indicates the need of an active program for their terminal care employing every feasible palliative measure.

In the management of any patient with lung cancer it is first incumbent upon the family physician and the chest internist that they share with the surgeon the responsibility of decision as to surgical intervention. Therefore, they should be thoroughly familiar with both the indications and contraindications for surgery.

Although the findings that indicate inoperability have been taken up in the chapter on surgery, we consider it essential to list them here to emphasize to the practitioner and chest internist the importance of searching for such evidence. With this information at hand they will then be able to judge the advisability of surgery.

The presence of distant metastases from lung cancer contraindicate surgery in all but the rare instance when significant palliation may be secured surgically. The more common distant metastases and the indirect evidence that points to their existence are here enumerated. (When possible, biopsy of such lesions is desirable.)

1. Palpable firm and large lymph nodes in the cervical region or just behind the clavicle (the softer nodes are less likely to contain metastatic neoplasm, especially those felt in the axillary region).
2. A nodular or grossly enlarged liver.
3. Brain metastasis, often evidenced by a recent localized and persistent headache, nausea, vomiting, drowsiness, or more localizing symptoms or signs. Abnormal skull radiogram, lumbar puncture, or electroencephalogram will help to confirm such a diagnosis.
4. Bone metastasis anywhere, but more commonly involving a vertebral

body, rib, skull, or pelvis accompanied by history of localized and recurrent pain of recent onset and often with radiographic changes

5. Suprarenal metastasis with occult or full-blown manifestation of adrenal deficiency

The intrathoracic metastases that indicate inoperability are.

1 Paralysis of the left recurrent laryngeal nerve, in a patient with recent onset of hoarseness or where bronchoscopy shows vocal cord paralysis.

2. X-ray or other evidence of rib or other bony destruction

3 Esophageal constriction or displacement by lung cancer, often accompanied by dysphagia

4. Clinical and radiographic signs of pleural effusion, often bloody, and containing tumor cells (operable only on the rarest occasion)

5 Radiographic or clinical signs of superior vena caval involvement.

6 Signs of infiltration of the chest wall, brachial plexus, or of sympathetic chain accompanying apical sulcus tumor

7. Radiographic signs of definite hilar lymphadenopathy, separate from the primary pulmonary cancer

8. Radiographic or clinical signs of bilateral mediastinal lymph node enlargement accompanying a known lung cancer.

(Paralysis of the phrenic nerve does not necessarily indicate inoperability if the lesion is otherwise operable, likewise hemidiaphragmatic paralysis does not necessarily indicate malignant invasion of the nerve)

9 Bronchoscopic findings of marked widening of the carina at the tracheal bifurcation, with inflexibility of the lower trachea and main bronchi or definite bronchial fixation, are generally due to mediastinal metastases

10 Bronchoscopic evidence of invasion of the trachea

In evaluating the possible significance of any one of these findings, the clinical picture as a whole must be taken into consideration before one decides that the lesion is definitely inoperable In borderline cases, scalene node biopsy and excision of some upper mediastinal connective or lymphatic tissue through a cervical incision may be recommended

It is furthermore the particular responsibility of the general practitioner and chest internist to appreciate the operative risk when a question exists regarding the patient's general condition The possible benefit derived from surgery must naturally be considered in relation to the hazards involved The operative risk is often dependent to a great extent upon the presence of a complicating disease such as serious heart disease, especially in the presence of heart failure (unless a good response to medical therapy is obtained) A history or electrocardiographic evidence of old coronary occlusion is not in itself a contraindication Critical

TABLE XIV

Palliative Measures in Inoperable Bronchogenic Carcinoma

Pathologic Physiology	Clinical Symptoms	Radiotherapy	Surgical Therapy	Medical Therapy
Bronchial proliferation and obstruction	Cough Dyspnea Wheezing Hemoptysis	Palliative x ray therapy (3000 r) [illegible] Radon seeds Telecurie therapy Co^{60} Multi million volt x rays Radioactive colloidal gold (Au^{198})	Bronchoscopic drainage ful[illegible]	Nitrogen mustard (HN_2)—0.1 mg. kg. I.V. [illegible] ustard [illegible] drugs [illegible]
Pulmonary infection	Fever Chills Cough Expectoration Malaise Toxemia	Radiation therapy to blocked bronchus and to compressing nodes for aeration and drainage	Bronchoscopic fulguration for drainage Thoracotomy for empyema Palliative resection for abscess or necrosis	Nitrogen mustards To relieve obstruction To allay toxemia Postural drainage Bronchodilator drugs Antibiotics
Local invasion	Pain	Radiation therapy	Neurosurgery *	? Ethyl chloride spray ? Local procaine injection ? I.V. alcohol 5 10 per cent Narcotics with Thorazine
Pathological fracture	Pain Disability	Roentgen therapy	Orthopedic measures	I.V. nitrogen mustard ? Procaine injection
Advancing neoplastic disease	Malnutrition Weakness Anxiety Insomnia Anorexia	Radiation therapy 1000 r to multiple areas		Nitrogen mustards High caloric diet I.V. glucose amigen Vitamin supplements Testosterone Cortisone or Meticorten Transfusions
Hypoadrenalism due to metastasis	Asthenia			Cortisone Sodium chloride DOCA
Brain invasion	Hemiplegia etc	Conventional roentgen therapy Marks grid High energy x ray therapy		Nitrogen mustard
Hemoptysis	Anemia Weakness	Roentgen therapy ? Cauterization	Emergency resection if fulminating	I.V. nitrogen mustard, medical measures
Pleural effusion	Dyspnea Disability	Roentgen therapy Intrapleural radioactive colloidal gold (Au^{198})	Pleural resection	Thoracentesis intrapleural nitrogen mustard Au^{198}
Superior vena cava compression syndrome	Severe cyanosis Dyspnea Orthopnea swelling of head and neck Complete disability	Radiation therapy		I.V. nitrogen mustard Oxygen Dehydration with Mercuhydrin Diamox Ammonium chloride
Radiation sickness	Loss of appetite nausea vomiting, weakness			DOCA Pyridoxine Replace electrolytes and water ACTH Cortisone Thorazine
Nitrogen mustard sickness	Nausea Vomiting			Sedation Cortisone ACTH Thorazine

* The measures cited as questionable have not proved useful in our hands although they have been mentioned as effective by other workers

SUPPORTIVE MEASURES

Maintenance of *morale* by attention to adequate psychotherapy heads the list of supportive measures for the patient with inoperable cancer Some of the means of encouraging and stimulating these patients will be outlined in the chapter on psychological aspects We have found that frequent careful questioning and thorough physical examinations are essential, so that medication can be given promptly for each new complaint. The beneficial as well as undesirable effects of drugs should be discussed openly to acquaint the patient with the underlying reasons for their use. One should not hesitate to change the drugs or their dosage frequently, and to enlist the help of the patient in evaluating each new regime We must remember that there will always be specific complaints and usually specific causes for them These are not only a challenge to our therapeutic skill, but present many stimulating diagnostic problems resulting from the extension of the disease Without an open and searching approach we can expect little effect from the medications we employ

For advancing neoplastic disease with progressive *malnutrition*, high caloric intake should be aimed at although its administration presents many difficulties Oral administration of fat emulsions combined with glucose have not been effective in our hands The use of vitamin supplements may prove helpful and are apparently more effective if given intravenously. The development of anemia should be anticipated and treated with iron, liver, B_{12}, and transfusion if necessary

Patients with lung cancer, unlike those with gastrointestinal cancer, rarely present problems in fluid and electrolyte imbalance The administration of intravenous glucose and protein hydrolysate solutions should be given sparingly It is of interest that cortisone given for brief periods of time often improves the appetite and general well-being If given at all, we suggest giving it in divided dosages, as follows 200 mg total daily dose for two days, 100 mg for two days, 50 mg. for two days, 25 mg for two or more days. Nausea may be a distressing symptom, and again a short period of cortisone therapy may be helpful At times, Prednisone® in place of cortisone may be tried, in dosage of 10 to 20 mg four times daily Its indications and effects are similar to cortisone, except that side reactions are fewer and of lesser degree, sodium and water retention are less of a problem Occasionally the administration of testosterone results in surprising improvement in well-being

The use of chlorpromazine (Thorazine®) in dosages of 50 mg every four to eight hours has occasionally proved of value in controlling nausea and vomiting, however, it has been more effective in augmenting the

sedative effect of barbiturates. Derivatives of rauwolfia serpentina can be given two to three times a day in an effort to control anxiety.

A word of caution about overtreatment is in order. Continued and vigorous use of parenteral solutions should be avoided. Attempting to correct hypoproteinemia by protein infusions is chiefly wasteful and expensive. We have already indicated that we usually do not advocate neurosurgery for the control of pain.

Attention to the care of the patient with inoperable lung cancer as outlined above yields satisfying rewards. Although life is not significantly prolonged, the patient can be made more comfortable. Not infrequently he is able to return to work for long periods and can maintain a hopeful if not entirely cheerful outlook with regard to his health status. Ideally, he should be working part or even full time as long as feasible. This has and can frequently be achieved by meticulous attention to all his complaints. A great contrast will then be seen to exist between the patient so handled and one who, through his physician's indifferent, frustrated, and careless attitude, has come to recognize the hopelessness of his disease.

17

Secondary Cancers of the Lung

Bernard Roswit
and John LaDue

INTRODUCTION

Until the present decade, there appeared to be little that could be done to help the patient with metastasis to the lungs from primary cancer elsewhere. Today, the probability of providing relief from pulmonary distress, prolongation of useful activity, and longer survival has been materially improved, especially in radiovulnerable and endocrine dependent neoplasms. This is largely the outcome of recent impressive developments in roentgen treatment, nuclear medicine, radical surgery, chemotherapy, hormone management, and supportive measures.

In this chapter we shall discuss the ominous complication of metastasis in relation to incidence, dynamics of pulmonary invasion, diagnostic problems, radiographic manifestations, and palliative management. We shall stress the value of a positive and more energetic treatment policy. Individuals with this complication are entitled to the same basic medical and humanitarian considerations as patients with other serious chronic and debilitating lung diseases.

INCIDENCE

It has been estimated that at least 25 per cent of all patients with cancer will have pulmonary metastases sooner or later in the course of the disease. Respiratory symptoms represent the major problem in about one-third of the individuals in this group (28). In this country alone, there are 20,000 new patients each year in need of effective palliative measures. From present trends it appears with certainty that this figure will continue to rise because of a) introduction of mass chest film surveys for the general public, b) follow-up studies of patients treated

for malignant disease, c) routine chest films for all hospital admissions, and d) wider application of more radical surgery and radiotherapy, with prolongation of life span and more time for spread to the lungs.

A recent analysis of 1000 autopsies of cancer patients by Abrams and his colleagues (1) revealed lung invasion in 46.5 per cent of the cases. Pulmonary invasion is noted in approximately 75 per cent of patients with renal carcinomas, 65 per cent in malignant melanoma, 58 per cent in breast carcinoma, 40 per cent in sarcomas, 20 per cent in cancer of the mouth, pharynx, stomach, liver, and pancreas, and 15 per cent in cervical cancer (39). Although skin cancer is one of the most common of all malignant lesions, pulmonary metastasis is rarely observed. We ha treated more than 1000 patients with skin cancer, without noting a sing instance of pulmonary spread, except in malignant melanoma.

DYNAMICS OF PULMONARY INVASION

The high incidence of metastatic cancer in the pulmonary field is not remarkable if one considers the strategic position of the lungs athwart the main stream of the venous circulation. Its vast capillary network provides an elegant filtration system with a high probability for malignant microembolism. Continuous respiratory movements lend further encouragement to the intrapulmonary spread of those neoplastic cells which gain a foothold in the pulmonary parenchyma.

There are several interesting channels by which malignant cells may reach the pulmonary bed: 1) direct tumor invasion of a contiguous major venous channel, as in carcinoma of the kidney, thyroid, and head and neck, 2) involvement of regional nodes with secondary breakthrough to venous channels, as in carcinoma of the breast and bronchus, 3) invasion of the lymph circulation to reach the thoracic duct, left subclavian vein, right auricle, and thence to the pulmonary bed, as in testicular neoplasms, 4) penetration of the vertebral veins connecting with all of the major venous systems, as in cancer of the prostate, 5) via the hepatic veins to the right auricle after temporary arrest at the liver, as in carcinoma of the gastrointestinal tract, 6) direct invasion of the lungs by contiguity from primary lesions in adjacent structures, as in cancer of liver, esophagus, stomach, mediastinum, pleura, pericardium, and musculoskeletal structures, 7) intraluminal spread from an ulcerating endobronchial lesion, necrotizing lymph node, or carcinoma of the head and neck, as in neoplasm of the tonsil, pharynx, bronchus and breast, 8) direct passage through the diaphragm via lymphatics from tumors of the abdominal cavity, seen in gastric carcinoma and retroperitoneal sarcoma.

A variety of other mechanisms for pulmonary spread have been described in detail by Willis (60, 61), who reminds us that not all tumor

emboli survive in the lung The sterile or abortive fibrosed tumor deposits occasionally seen in sectioned lungs prove that metastasis may be something more than a purely microembolic phenomenon.

Once securely established on the pulmonary beachhead, the rapidly proliferating cells become reinforced for a final and overwhelming assault, invading at various intervals the parenchyma, bronchial tree, intrapulmonary lymphatics, great vessels, and pleura

DIAGNOSIS

The Importance of Early Diagnosis

Early diagnosis of metastatic lung cancer is of far more than academic interest, because 1) distant metastasis must be excluded before subjecting the patient to radical treatment of a primary neoplasm, 2) solitary metastatic lesions, in several well-documented cases, have been successfully resected, and the patient apparently freed of malignant disease (9, 26, 34, 52, 56), 3) metastatic lung cancer may be the first warning of the presence of a silent primary neoplasm, 4) removal of the primary cancer has, on rare occasions, brought about a disappearance of the secondary lung disease and prolongation of useful life, and 5) palliative measures, specific and supportive, are far more effective when instituted early in the course of the malignant process

Clinical Picture

There is no clinical pattern characteristic of pulmonary metastasis The symptoms and signs are governed by the anatomic site of invasion and by the type of physiologic disturbance created Early metastatic lesions in the lung are almost invariably silent and undiscovered except by radiographic examination Today, in the era of mass chest surveys, it is not at all uncommon to find individuals with well-established lung invasion completely unaware of the primary and secondary disease they are harboring In such cases, an exhaustive search for the primary neoplasm is indicated, governed largely by the relative frequency of pulmonary metastasis from principal primary sources, according to the age of the patient

As the neoplastic process advances, there will soon be symptoms of a general nature such as anorexia, malaise, weakness, weight loss, chest pain, dyspnea, and cough Hemoptysis is a truly important symptom in this period Abnormal physical findings are rarely present until late in the disease, and are characteristic of the particular functional pathology present They have been well described by Karnofsky, Myers and Phillips (28).

Massive nodular disease may interfere radically with alveolar-capillary

exchange through obliteration of the basic pulmonary unit. Parenchymal lesions extending to the pleura will soon produce pleural effusion, leading to inadequate alveolar ventilation and dyspnea. Extension into the bronchus may lead to atelectasis, pneumonitis, and abscess formation with all of the unpleasant symptoms attending a chronic unrelenting lung infection. Carcinomatous endarteritis may obstruct the pulmonary blood flow and produce pulmonary hypertension and *cor pulmonale* (55). In a large parenchymal mass, central necrotization and cavitation may occur, simulating a benign abscess or peripheral bronchogenic carcinoma.

One of the most distressful of all clinical syndromes is that arising from compression of the superior vena cava by the neoplasm. We have seen several examples of this entity in carcinoma of the thyroid, breast, ovary, testicle, and in the malignant lymphomas. It is particularly common, in our experience, in anaplastic bronchogenic carcinoma. The superior vena cava lies in a highly vulnerable position between the anterior prevascular lymph nodes and the right paratracheal nodes which are very frequently involved by neoplasms invading the thorax.

Laboratory Studies

In a patient with a parenchymal nodule or infiltrate and a known primary neoplasm elsewhere, there would appear to be little need to pursue a histologic diagnosis of the pulmonary disease with too much vigor. However, we are reminded by Cahan (5) that multiple primary cancers in unrelated systems can and probably will occur with increasing frequency as survival rates improve. There is approximately a three-and-one-half-to-one chance that a solitary pulmonary shadow is a separate primary lung cancer rather than a single metastatic deposit, particularly in cancer of the head and neck (5).

Cytologic examination of sputum, tracheal washings, gastric lavage, and bronchial washings may be helpful on occasion in establishing the true nature of the pulmonary density. Bronchiolar carcinoma, for example, often simulates metastasis arising from other primary sources but can be detected by the Papanicolaou technique in a remarkably high percentage of cases.

Radioisotope tracer techniques can be of service in detecting the presence of thyroid metastases. In approximately 15 per cent of patients with thyroid cancer, the primary and metastatic growth will prove to be of the "functioning" type, producing colloid and concentrating iodine. When pulmonary infiltrates appear in a patient previously treated for thyroid cancer, the true nature of the lesions may sometimes be determined with I^{131}. However, failure to concentrate radioiodine does not necessarily exclude the possibility of metastatic lesions springing from the thyroid, because: 1) the suspected infiltrate may be of a different

histologic variety of thyroid neoplasm than the primary growth, or 2) in the presence of remaining normal thyroid tissue, there will be little or no I^{131} left for the metastases. In such cases, the thyroid gland may be completely ablated by surgical means or destroyed with a large dose of orally or intravenously administered I^{131}. The subsequent administration of thiouracil or thyroid-stimulating hormone may further serve to stimulate the uptake of I^{131} in the lung tumors.

Bronchoscopic examination will provide material for exfoliative cytology and occasionally will disclose an endobronchial proliferation. Certainly, when widening of the carina is observed during bronchoscopy, there is established at once the presence of malignant disease and the non-resectability of the growth.

RADIOGRAPHIC CONSIDERATIONS

It is the radiologist who must shoulder the principal burden of responsibility for the early detection of metastatic lung cancer because this disease is seen by radiography long before there are any symptoms or physical signs. Nevertheless, the limitations of early roentgen diagnosis are such as to discourage dogmatism and to stimulate pursuit of more precise means of identification. It is possible however to recognize certain general radiographic patterns so that the true nature of the process can be suspected. The individual characteristics of these patterns will be briefly discussed, noting specific examples and indicating some of the problems in differential diagnosis.

1. *Nodular* discrete shadows may be solitary, multiple, dense, homogeneous, widely distributed, more numerous in the lower lung fields, with variations in size according to the stage of development, and rapidly increasing in size and number. Although these lesions occasionally appear to be solitary on x-ray examination, multiple foci are nearly always found at exploratory surgery (34). When less than 3 mm. in diameter they do not produce a recognizable roentgen shadow. Laminographic studies are helpful, particularly when there is a decision to be faced as to resectional surgery. In this connection, the use of supervoltage x-rays (1 Mev) has been proposed to detect such early lesions obscured by skeletal parts, and often centrally located (58). The best examples of the nodular type of invasion are to be found in neoplasms of the testicle, kidney, and colon, and in chorioepithelioma, soft tissue sarcoma, osteogenic sarcoma, and malignant melanoma. If metastatic malignancy is strongly suspected and the original growth remains silent, the organs most likely to be involved should be investigated first. Wilms' tumor and neuroblastoma are common in children up to the age of seven years; teen-agers are likely to be harboring a malignant growth of bone or malignant lymphoma; in the third decade, one should search first for a testicular neoplasm, malig-

nant melanoma, or soft tissue sarcoma; and above the age of 40, cancer of the breast and cancer of the stomach predominate.

2. *Miliary* lesions are seen occasionally in cancer of breast, pancreas, and in other neoplasms Differentiation must be made from miliary tuberculosis, pneumoconiosis, fungus disease, and chronic bronchiolitis.

3. *Linear infiltrating* densities radiate bilaterally from the lung root along the bronchovascular trunks. Secondary endarteritis in such cases may produce typical *cor pulmonale.* The linear variety is most common in metastatic cancer of the breast and stomach, and gives rise to severe dyspnea when advanced. When these changes are seen in a previously irradiated area, differentiation from radiation fibrosis is obviously essential Radiation changes are unilateral and sharply limited to the irradiated zone. They are frequently associated with retraction of the mediastinum and tenting of the diaphragm. The time/dose treatment factors, period of onset, and associated symptoms, must all be considered in the differential diagnosis.

4. *Pleural* involvement may be characterized by nodular implants, diffuse thickening, or intractable effusion. This complication may occur in all primary new growths, but especially in carcinoma of the bronchus, breast, and ovary, and in Ewing's tumor. Differential diagnosis must include an unlimited variety of benign disease entities as well as such primary neoplasms of the thorax as mesothelioma, fibrosarcoma, and osteochondrosarcoma Tomography, vertical and horizontal, is quite helpful

5 *Hilar and mediastinal lymph node* masses are most frequently seen in the malignant lymphomas Benign lesions must be excluded, such as dermoid, neurofibroma, paravertebral abscess, inflammatory nodes, Boeck's sarcoid, dilated esophagus, and intrathoracic thyroid. The latter can be quickly recognized by means of a radioiodine profile study. A scintiscanner can be utilized to delineate the landmarks of the thyroid tissue with precision

6 Various *secondary changes* may develop including bronchial stenosis, atelectasis, and obstructive pneumonitis. Differentiation from primary bronchogenic carcinoma by x-ray may be virtually impossible under such circumstances

7. *Cavitary* lesions are occasionally seen in Hodgkin's disease, and in tumors of the "cannon-ball" type with central necrotization

Pulmonary involvement in the malignant lymphomas deserves special consideration. A study of this complication was recently undertaken in our clinic (B R.) (43) We were impressed by the high incidence, infinite variety of radiographic appearance, and response to treatment by roentgen rays and nitrogen mustard We have observed peribronchial and endobronchial infiltrates, massive homogeneous lobar tumors, lobular infiltrates, and generalized dissemination characterized by true miliary

and lymphangitic spread. Parenchymal infiltration occurred somewhat late in the course of the disease and progressed fairly rapidly, being always associated with mediastinal nodes except in rare instances

The lungs are one of the most common sites for metastases from breast cancer Almost all the patients dying of advanced carcinoma of the breast have pulmonary metastases at autopsy, and in approximately half of the patients these lesions appear as soon as, or together with, metastases to other sites The foci may appear in the lung parenchyma or the mediastinum, or present themselves as a pleural effusion Not uncommonly, the spread is lymphangitic and may involve both lungs simultaneously The only x-ray changes then observed are increased bronchovascular markings Clinically, pulmonary metastases from breast cancer may escape detection unless a chest x-ray is done More frequently, the patients complain of dyspnea or develop a dry hacking cough that is brought on by a change in position Physical examination may reveal no abnormalities, except evidence of bronchospasm with wheezing. The metastases may further result in pleural effusion or may even be confused with pneumonic consolidation of the lung.

An extended discussion of these and other important individual neoplasms is beyond the scope of this chapter

TREATMENT

No patient with metastatic lung cancer should ever be denied serious consideration for palliative measures that may provide respite from distress and disability, prolongation of useful activity, or a chance for prolonged control of his malignant disease Such measures have recently become available to every physician What is most needed today, however, both in undergraduate training and in clinical practice, is an active and more positive approach toward the management of such patients, despite their present meager probability for survival There is much to be gained from such an attitude, for physician and patient alike

Whether treatment should be specific or supportive, radical or conservative, depends upon the histology of the malignant process, the status of the primary lesion, the extent of the metastatic process, and the general condition of the patient *Specific* therapy has the ability to destroy or inhibit malignant growth The selection of a particular agent for this function—surgery, roentgen therapy, radioisotopes, chemotherapy, or steroids—rests principally upon the histology and extent of the metastatic process

Supportive therapy ...
consolation and peace ...
physician

SURGERY

Complete surgical extirpation (wedge resection, lobectomy or pneumonectomy) of a secondary lung lesion may be undertaken if there is a solitary circumscribed nodule in a patient whose primary lesion has long been controlled. While over-all results of surgery have been discouraging, there are now several reports of prolonged arrest of the disease through such an approach, particularly in slow-growing osteogenic sarcomas and soft tissue sarcomas (9, 26, 34, 52, 56). In selected cases, resection of regional nodes or even skeletal structures (rib, clavicle), may be effective in bringing about a long survival period.

What should be done about the problem presented by the patient with a solitary, asymptomatic pulmonary lesion who has no history of previous malignant disease? Experience has proven that there may be grave danger in "watchful waiting." The incidence of primary and secondary cancer in solitary lesions varies from 15 per cent to 50 per cent. Preoperative diagnostic studies are generally unreliable for establishing their exact nature. On the other hand, such lesions may be safely removed today by surgical means and the diagnosis rapidly established. Whenever there is doubt—"operate."

Meckstroth, Andrews, and Klassen (34), supporting such a program, report malignant lesions in 38.5 per cent of 70 operated patients, of whom 15.7 per cent had bronchogenic carcinoma and 17.1 per cent had metastatic carcinoma or sarcoma. In two patients with no knowledge of an extrathoracic primary lesion, primary growths were found and removed, with excellent palliation and prolongation of useful life.

ROENTGEN THERAPY

Gratifying benefits, both subjective and objective, may be achieved through roentgen therapy in patients with metastatic lung disease, providing the lesion is in either a radiosensitive or a radioresponsive category. There is little to be gained in the treatment of metastases of known radioresistance such as those from the gastrointestinal tract, pancreas, adrenal, gall bladder, osteogenic sarcoma, soft tissue sarcoma, or malignant melanoma, particularly if they are asymptomatic.

In the radiosensitive group (Wilms' tumor, Ewing's tumor, malignant lymphomas, chorioepithelioma, neuroblastoma, oat cell bronchial cancer, etc.), the prompt and dramatic radiation response often observed may raise false hope for prolonged survival. Unfortunately, radiosensitivity and radiocurability are not necessarily synonymous. However, long survivals of five years or more have occasionally been observed in this group in our own clinic and elsewhere.

In the radioresponsive group (hypernephroma, cancer of the breast,

cervix, and thyroid, and epidermoid carcinoma of the head, neck, bronchus, and esophagus), the palliative benefits of roentgen therapy are less striking but nonetheless worthwhile Radiation can frequently provide relief from hemoptysis, dyspnea, orthopnea, cough, expectoration, and chest pain, and regression of atelectasis, fluid, and parenchymal infiltrates, as well as healing of pathologic fractures

Despite its threatening character, the superior vena cava compression syndrome will often yield to radiotherapy if the lesion is of a radio-vulnerable type For example, one of our patients with Hodgkin's disease has had a four-year remission of this complication after a tumor dose of 2700 r to the mediastinum Another individual with anaplastic thyroid cancer has survived more than ten years without disease after a tumor dose of 4000 r to the superior mediastinal mass (Fig 150)

Prolongation of social and economic usefulness is often feasible with a well-planned combined treatment program in patients with cancer of the breast, prostate, and thyroid, whose management by other specific methods will be described in another section

Palliative roentgen treatment is administered according to the principles and techniques outlined in the chapter on radiotherapy, with certain modifications Since a large volume of lung tissue must be exposed to the beam in disseminated disease, one should not generally exceed a maximum tumor dose (at the midsagittal plane) of 2500 r in about 3 weeks. Large paired opposing portals are almost invariably required A single lesion or lobe or lung may be first irradiated in a trial effort, choosing the more involved lung first

At this dose level, local and systemic complications are not usually severe and symptomatic radiation pneumonitis is rarely seen The lung reaction, however, remains the most critical limiting factor in our ability to restrain the growth of the malignant tumor There is little doubt that larger tumor doses in the range of 4000 to 5000 r in four to five weeks would provide greater palliation However, the greater risk of severe impairment of respiratory function is not justified in a palliative procedure Although encouraging clinical data is still meager, there is some hope that cortisone may control radiation pneumonitis (7, 15, 59) Our patients are routinely given hydrocortisone in 60-mg daily doses before, during, and for several weeks after roentgen therapy Antibiotics are also administered for the prevention of secondary infection

Conventional apparatus (200–260 Kev) is entirely satisfactory for palliative therapy of metastatic lung cancer However, higher energy radiation (1–2 Mev), has, in our experience, provided some practical clinical and physical advantages, including greater reaching-power to the deep-seated lesion, less skin effect, minimal radiation sickness, and greater homogeneity of dosage in the extensive tumor area

Roentgen therapy is most effective in pulmonary lymphomas, notably in Hodgkin's disease of the thorax (*10, 12, 24, 53*). Such lesions are somewhat less radiosensitive than Hodgkin's lesions elsewhere. In the mediastinum, however, they may yield permanently to a tumor dose of about 3500 r in four weeks Radical dosage in lymphomas with this limited involvement appears justified, in selected cases. Such a program has been adopted in our clinics Parenchymal lesions are almost invariably accompanied by generalized disease elsewhere. In such cases, less aggressive treatment is given, in the range of 1500–2500 r.

A more complete consideration of each of the principal malignant diseases cannot be undertaken within the limits of this chapter.

Chemotherapy

Nitrogen mustard (HN_2) and triethylene melamine (TEM) have become, in our experience, helpful adjuncts in the management of metastatic lung lesions, particularly those in the radiosensitive category (malignant lymphomas, anaplastic or oat cell bronchial carcinoma, neuroblastoma, Wilms' tumor, and chorioepithelioma) They have also been utilized, with sporadic and inconsistent benefit, in a variety of other neoplastic diseases with spread to the lungs. Their use in bronchogenic carcinoma has been discussed in detail in the chapter on chemotherapy and elsewhere (*27, 32, 33, 46, 47, 48*)

These agents, radiomimetic in character, act upon rapidly proliferating tissues and inflammatory processes, producing tissue changes in the tumor such as those seen after small doses of roentgen therapy. However, in therapeutic doses, the effects of these drugs differ from locally administered roentgen therapy in greater systemic toxicity, narrow margin of safety, relatively brief remission periods, irreversible bone marrow damage, and inability to destroy or materially inhibit the further growth of the malignant lesions.

Despite these limitations, intravenous HN_2 and oral TEM have provided significant subjective and objective benefits in a majority of the patients treated. HN_2 or Mustargen® is by far the more effective agent of the two, being prompt and fairly consistent in its therapeutic action. Both drugs become less helpful as treatment courses are repeated Their use is contraindicated in patients with persistent leukopenia, thrombocytopenia, or other evidence of bone marrow depression

Generalized malignant lymphomas with pulmonary infiltration may respond dramatically to nitrogen mustard In this group it is employed as an adjunct to roentgen therapy in the control of massive mediastinal disease, in the superior vena cava compression syndrome, and in patients with bilateral, diffuse pulmonary infiltration There appears to be no

logical means of predicting the response of a specific lymphomatous lesion to therapy. In general, one may expect much better results in Hodgkin's disease than in lymphosarcoma, while the reticulum cell variety may be quite resistant.

In the chronic leukemias we have seen pulmonary invasion only infrequently and very late in the course of the disease. It may be successfully managed by the use of HN_2, TEM, P^{32}, myleranar, urethane. Mediastinal lymphadenopathy in chronic leukemia is best treated with roentgen therapy.

Nitrogen mustard has resulted in considerable improvement in the respiratory status of patients with lymphangitic lung lesions secondary to breast cancer.

For a discussion of the dosage and technique of intravenous nitrogen mustard administration, reference should be made to the chapter on chemotherapy and to other communications on this subject (27, 32, 33, 46, 47, 48).

We have noted disappearance of pleural effusion in secondary lung cancers following the intrapleural instillation of 20 to 40 mg of nitrogen mustard, 0.4 mg per kilogram of body weight. The pleural space is tapped as dry as possible and nitrogen mustard (diluted with 100 cc of saline) is reinjected into the pleural space. Approximately 50 per cent of patients so treated will not develop recurrent pleural fluid. This is a level of effectiveness at least as satisfactory as that accomplished with radioactive colloidal suspensions.

ENDOCRINE THERAPY

Breast Cancer

It is well recognized that effective palliation can be achieved in some patients with advanced breast cancer by creating alterations in endocrine balance. Pulmonary metastases share in this response to hormonal control which is accomplished by the use of estrogens, androgens, surgical and roentgen castration, and to a lesser extent, by adrenalectomy and hypophysectomy. The criteria for the selection of the optimal therapy for the individual patient are not yet well established. Present treatment is based largely on the menstrual status and on the type of breast cancer—one being dependent upon estrogen for maintenance of growth and the other non-estrogen dependent.

In premenopausal patients (Fig 147), pulmonary metastases may sometimes be controlled by means of castration (by surgery or x-ray) or through the use of androgens in doses of 100 mg of testosterone propionate injected intramuscularly three times weekly. The subjective and

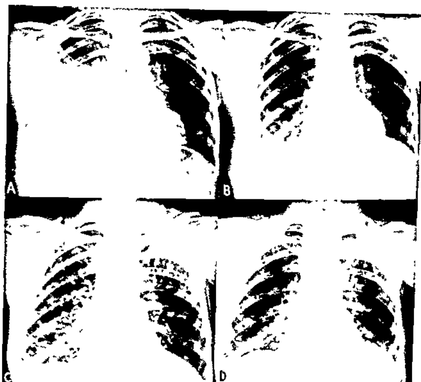


Fig 147 Metastatic breast cancer Premenopausal testosterone therapy

A Case 1 Massive pleural effusion in 42-year-old female before therapy

B Complete disappearance of fluid in same patient after administration of 10 g testosterone in 18 weeks Patient still well three years later despite treated relapse in the second year of illness

C Case 2 Diffuse nodular metastases of varying size in both lung fields before therapy

D Note striking improvement in same patient five months later following administration of 12 g testosterone propionate

objective improvement thus gained may last from several weeks to several months Upon relapse, discontinuation of the drug may bring about further improvement In such patients, adrenalectomy may result in further benefits in approximately 50 per cent of the cases. Hypophysectomy may prove to be useful in controlling pulmonary metastases, but experience is still limited In patients refractory to castration and to testosterone as well, cortisone may provide temporary gains (Fig 148)

In postmenopausal women (with menopause at least ten years previously), estrogen therapy is apt to produce regression of pulmonary metastases (Fig. 149), while in younger women there is a one-in-five

Fig 148 Metastatic breast cancer Postmenopausal cortisone therapy

A Case 5 Nodular involvement of the pulmonary parenchyma associated with pleural effusion

B Clearing of lung fields with small amount of residual fluid six months after administration of cortisone

chance of accelerating the disease Oral doses of ethinyl estradiol and diethyl Stilbesterol may be given daily in cycles of 40 days on and 10 days off medication Certain safeguards must be employed, such as a low sodium diet, since estrogens, like androgens, produce retention of salt and water When relapse occurs, androgens, castration, combined adrenalectomy and castration, and cortisone are used in a variety of sequences in different clinics (16, 37, 40)

Patients with non-estrogen dependent breast cancer are not helped by castration and are probably not benefited by adrenalectomy Pearson and his colleagues (38) have induced objective remissions in such cases by means of cortisone in doses of 200–300 mg per day

In males with cancer of the breast and pulmonary invasion, orchiectomy can be remarkably effective for long periods Upon relapse, estrogen therapy can be introduced As in female breast cancer, adrenalectomy and hypophysectomy may eventually have to be utilized for further control of the disease process

In the pursuit of the ideal hormonal treatment formula, it should not be overlooked that roentgen therapy remains a reliable and fairly consistent modality for controlling mediastinal nodes, parenchymal infiltrations, pathologic fractures, and recurrent pleural effusions In any event, there is available today a broad spectrum of useful agents for successful palliative management of this disease Skillfully employed, they will make it possible for some of these unhappy patients to live a life of social and economic usefulness There are no patients more grateful

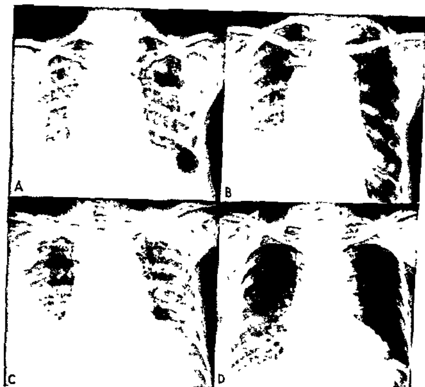


Fig 149 Metastatic breast cancer Postmenopausal estrogen therapy

A Case 3 Multinodular pulmonary metastases in both lung fields in 65-year-old female before treatment

B Note clearing of both lung fields during administration of di-ethylstilbesterol Remission lasted a total of five years, after treated relapse in the third year

C Case 4 Note massive invasion of both lung fields with linear infiltrate as well as nodular densities, before therapy

D Clearing of pulmonary metastases after estrogen therapy

Prostatic Cancer

Pulmonary metastases are not common in prostatic cancer. The administration of estrogens, orchiectomy or combined orchiectomy-estrogen therapy will frequently bring about regression of pulmonary or osseous metastases and will prolong useful life *Cyclic administration of estrogens* is suggested, to obviate the mastodynia and gynecomastia that follow unrelenting estrogenic stimulus to breast tissue. Clinical improvement, characterized by gain in weight, strength, appetite, and well-being, with improvement of hemoglobin and red blood count, will last for variable

periods up to two years in the majority of the cases. About 20 per cent of the patients will live in reasonable comfort for variable periods up to ten years under hormonal control. Upon relapse, cortisone therapy, bilateral adrenalectomy, and even hypophysectomy may need to be considered.

RADIOISOTOPE THERAPY

The role of the radioactive isotopes in the treatment of primary metastatic bronchogenic carcinoma has been discussed in the chapter radioisotopes. Metastatic lung cancer from other primary sources m also be treated by employing the same nuclear agents, rationale, and techniques previously described. They include intrapleural, interstitial, endobronchial, intravenous, and telecurie therapy methods (2, 4, 18, 21, 22, 25, 35, 36, 43, 45, 49, 54, 62).

The pulmonary metastases from thyroid cancer respond to I^{131} therapy but not quite as favorably as the skeletal lesions. The therapeutic management of such cases follows the same pattern described in the section on diagnosis for inducing the improved uptake of I^{131}. Despite more than ten years of intensive activity in this field, each new case continues to require an experimental approach. Evaluation of results is difficult because of the unpredictable life history of the disease. However, it has been definitely established that unless the histology of the lesion is of the alveolar or follicular type, radioiodine treatment may be fruitless.

Our experience has shown that those patients unsuitable for radioiodine treatment may respond very well indeed to intensive roentgen therapy. Such an instance is to be found in Case 6, Fig. 150.

The use of P^{32} in chronic leukemia deserves mention, for this agent, in carefully titrated dosage, has proven to be a convenient and effective method for handling this disease. Furthermore, there is some evidence that such a program may reduce hospitalization periods and the need for transfusions, and prolong useful life (39). Similar benefits have been gained from total body radiation.

Of recent interest has been the development of methods for inducing total ablation of the pituitary in patients with disseminated cancer in the lungs and elsewhere from primary lesions in the breast and prostate. Since complete ablation of the hypophysis by surgical means is not always feasible or successful, total destruction of the gland by means of ionizing radiation has been attempted. External roentgen therapy has proven ineffective for this purpose, even at the highest dose levels within the tolerance of the intervening brain tissue. Far more selective and intensive irradiation is now possible, utilizing interstitial radioactive sources. Tiny beads of radioactive palladium, yttrium, or gold have been directly

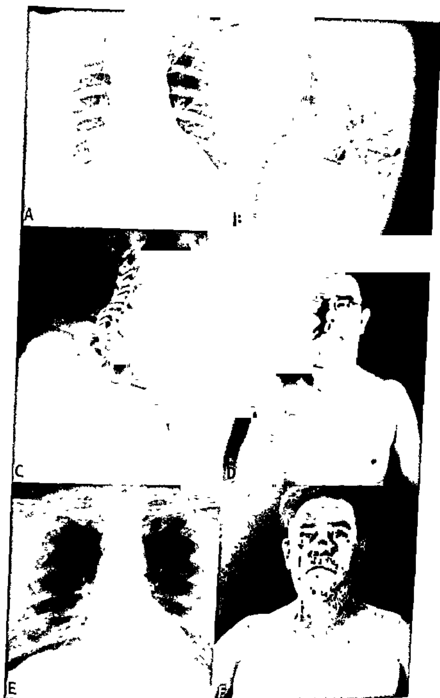


Fig 150 Metastatic thyroid cancer Radiation therapy.

A Case 6. Massive involvement of hilar, mediastinal, and cervical lymph nodes, with "cannon-ball" metastasis in right lower lung field. Patient is a 50-year-old



Fig 151. Metastatic Wilms' tumor Radiation therapy

A Case 7 Large "cannon ball" metastasis in the right lung field in 3½-year-old white male child with a Wilms' tumor of the kidney Note also other metastatic foci involving the lung and the left paramediastinal lymph nodes

B Complete clearing of the right lung field after 1850 r tumor dose in 12 days through two very large paired opposing portals However, note the enlargement of the left paramediastinal and parahilar lymph nodes in the untreated areas Courtesy of Dr James J Nickson, Memorial Hospital, New York City

introduced into the pituitary gland, producing total ablation without hazard to the surrounding normal tissue

In another study, conducted at the University of California, proton particles have been fired with infinite precision into the hypophyseal body by means of a high-energy particle accelerator (240 Mev synchro-

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white male first seen in 1945 with fulminating superior vena cava compression syndrome Histology—adenocarcinoma of the thyroid, Grade IV

B Lateral radiograph in same patient revealing anterior mediastinal lymph node mass and parenchymal tumor as well

C Note marked compression of the trachea by encircling metastatic cervical lymph nodes

D. Photograph of patient before treatment, revealing the "bull frog" facies, superficial venous collaterals, and cervicothoracic edema characteristic of the superior vena cava compression syndrome Patient suffered intensely from dyspnea, orthopnea, and syncope

E Complete disappearance of all metastatic lesions as well as the primary neoplasm of the thyroid after a tumor dose of 4000 r in six weeks administered by multiportal cross firing technique The pulmonary parenchymal lesion received 1800 r tumor dose

F Photograph of patient ten years following administration of roentgen therapy He is perfectly well, free from disease, and working full-time as a railroad conductor since the time of treatment

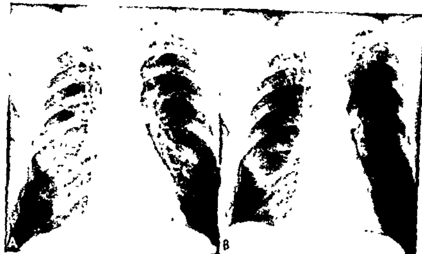


Fig 152 Metastatic renal carcinoma. Spontaneous remission after surgical removal of primary neoplasm

A Case 8 Large nodular metastases in both lung fields Small apical infiltrations represent old healed tuberculosis Patient was a 60-year-old white male with abdominal tenderness, right upper quadrant mass, and hematuria.

B Radiograph shows prompt and complete disappearance of all pulmonary metastases for ten months after removal of a clear-cell carcinoma of the right kidney, through the thoraco-abdominal approach Patient remains well and free from other metastatic foci

tron) In a relatively small number of patients, early clinical benefits have been reported, without serious untoward effects

SUPPORTIVE MEASURES

An impressive array of newer and more effective supportive measures has recently become available for relief of pain, dyspnea, and many other distressing symptoms. These symptoms add to the burden of suffering in patients intractable to specific therapy for their metastatic pulmonary disease. These agents, and the techniques by which they may be most advantageously employed, have been discussed in the chapter on medical management.

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away. These individuals who have had experience with cancer in friends or families may hold the belief that the longer a fruitless course of pain and suffering can be put off, the better off they are. If the threat is perceived as potentially overwhelming, some individuals deny the existence of even the symptoms, but more commonly, the patient makes his own and less threatening diagnosis. Such a patient must usually deny the need of adequate treatment and is quite hostile to those who attempt to force it on him. He is very prone to exhibit paranoid trends following treatment.

What looks like a realistic and prompt seeking of medical attention may in fact be a panicky flight for help of one who also feels himself overwhelmingly threatened. This type of patient may well deceive the doctor into believing that he is dealing with a "well-balanced" person, when in fact he is dealing with someone on the verge of disorganization.

How the individual has handled other life crises is not an infallible guide to how he handles the crisis of threat to his life. Few of life's crises, fortunately, are as threatening as cancer, a potentially fatal illness, or its surgery, extensive and productive of serious change in form and function (2, 3). The threat is highly unique. How it threatens is specific to the individual and is determined by its potential for disruption of long-established, strongly held, valued activities evolved in the individual's particular psychic development, that are basic to his emotional stability. For example, for many individuals the ability to meet life's crises is dependent upon a strong sense of their own invulnerability or their ability to control events. Thus the powerful executive who finds himself with cancer may approach panic because he is the victim of something he cannot control and which seriously attacks his invulnerability.

Surgery is frequently involved in treatment for carcinoma of the lung and the quality of the surgical experience, as with cancers of other sites, is of major importance in determining the individual's long-range adaptations. Most patients regard surgery as far more dangerous than it realistically is. This is especially true when cancer is the primary disease. Many people equate the seriousness of the surgery with the seriousness of the primary illness. A great many patients regard their chances for survival of any operation for cancer as no better than a "toss-up," a "fifty-fifty proposition." Fear of death in surgery is increased when organs of importance to the patient are operated upon. Consequently, one finds in those patients subjected to thoracotomy an even greater fear of death than is warranted by the nature of the surgery. (Lobectomy and pneumonectomy appear to carry a sufficient mortality to justify the fears of most patients.) Consequently, patients approach surgery, especially for cancer of the lung, with a considerable degree of apprehension, which focuses upon either death in surgery or the compromise of a vital physio-

logical system to such an extent that they will be unable to function in the future.

The respiratory function is so vital that any interference with it gives rise to considerable anxiety. In the popular mind breathing has become equated with life itself, as witness: "the breath of life," "as long as there is breath in my body." In many cultures the breath is equated with the soul. Moreover, breathing capacity is often equated with physical prowess. The physical measurement of chest expansion as evidence of healthy development has been until recent times an important part of many physical examinations. Stamina, "second wind," is often also associated with respiratory function. On the other hand, sickly individuals may have "weak lungs." Even the conventional medical term "vital capacity" testifies to the emotional respect with which this function is held.

The lungs are considered organs which must be protected and which in turn protect the body. The craving for fresh air has probably less to do with the oxygen content of the air than with the notion that such air will revivify or fortify the lungs and the whole body. The lungs are also seen as routes of infection apart from their realistic role. Bad air (Italian *malaria*) attacks the lungs and the integrity of the entire body.

In children, any interference with breathing arouses intense anxiety, manifested by a primitive sort of thrashing behavior and an endeavor to secure a clear airway. Nightmares which have the quality of suffocation or drowning are usually of particular horror.

Anxiety may be expressed by changes in the respiratory pattern. Mild anxiety can be manifested by slight variations in breathing as attested to by common expressions: "hold your breath," "it took my breath away." Marked anxiety may be associated with considerable variations in breathing patterns, such as intense sighing respirations and short periods of apnea. Anxiety attacks themselves may be manifested by intense dyspnea and may proceed to overventilation resulting in tetany. Chronic anxiety neurotics who focus on the breathing apparatus may experience dyspnea secondary to a shift of the mid-position of the chest, so that they are effectively breathing only with their complemental or supplemental air. These spirograms may be so distorted that they lead to significant errors in determining, for example, the basal metabolic rate (4).

Certain psychoanalysts believe that in some individuals breathing may be utilized as a sexual substitute, as a method of smelling, or even of incorporating a beloved object (5). Such integration is usually present when the direct expression has been inhibited by anxiety over the sexual function itself, which in turn has been related in conventional psychoanalysis to castration or punishment fears. Interference with breathing

in such cases may result in an evocation of the primary fears of castration or great physical punishment or mutilation.

Anxiety from any cause may decrease effective pulmonary ventilation in patients with lung disease, which leads to further anxiety, and in turn leads to further ventilation difficulties and so to the establishment of a vicious circle. It is not unusual to find, for example after thoracotomy, a patient so anxious about his breathing that he inhibits his normal excursion and consequently does not ventilate adequately.

Whenever an activity so important for survival as respiration is threatened by disease or by treatment for disease, then considerable anxiety will be aroused. Anxiety may in itself interfere with proper function of the system and favor development of patterns of behavior designed to protect the body. Insofar as they are based on false notions of physiology they may militate against the patient's well-being. It is important, therefore, not merely to relieve anxiety but to seek out and correct misconceptions of physiology on which the patient may base his behavior.

The quality of the terror associated with major surgery is exemplified by the nature of the dreams which frequently occur both preoperatively and postoperatively. These are of nightmare or even hallucinatory intensity. They are of death or mutilation which spell out explicitly the threat the patient foresees or believes he has somehow escaped. Parents who have been dead for thirty years or more may be resurrected in dreams to reassure the patient that he will be all right.

The postoperative period following pulmonary surgery is realistically a difficult one for most patients. Even in the uncomplicated case the postoperative course is sufficiently formidable to convince most patients that something serious has happened to them. Thoracotomy tubes and underwater drainage give ample support to the feeling that the body has been violated.

Control of pain is most important in this period. Chronic severe pain is realistically debilitating and in the chest wall interferes significantly with adequate pulmonary ventilation. It is, of course, a prime symbol of injury to the body or of continuing disease. It is also very important to allay anxiety which may interfere with respiration and ventilation.

Any postoperative complication has both a physical and a psychological threat. The period of invalidism is prolonged realistically and the sense of body injury is increased. Complications, even though they are nonspecific and are found in almost any type of surgery, such as thrombophlebitis, or specific complications, such as bronchopleural fistula with possible empyema, may well be identified by the patient as evidence of incomplete removal of the cancer or as surgical maladroitness. It is just as important psychologically as it is physically to prevent these compli-

cations, or to recognize them as soon as they develop, because they give rise to notions of profound body injury which later become the basis for prolonged invalidism The physician should search out the significance of the complication to the patient and actively correct misconceptions Most patients who have complications have unexpressed beliefs about them

Modern surgical practice recommends the early mobilization of the patient The psychological effects of early mobilization have not fully been evaluated If the patient is psychologically not ready to be mobilized and believes that activity will be damaging to his body, forced mobilization may generate considerable anxiety He may obey the physician while in the hospital, rise from bed and even walk the halls, but after discharge he will delay his return to useful activity because he feels that he has not been allowed sufficient time to regain his strength

Rather than be forced to get out of bed, the patient should be urged and encouraged to do so Clinical experience suggests that permissive ambulation does not result in a longer period of hospitalization for each patient, and may indeed result in a shorter period of over-all invalidism Reluctance to move from bed may represent very real fear of the ability of the body to withstand the trauma of such activity The patient does not know the extent of injury to his body and to its functioning, and must assay this damage by gentle and cautious testing Such restriction of activity is rarely due to a desire for neurotic "secondary gains," such as attention attracting, or the satisfaction of desires for self-dramatization or avoiding responsibility

Childish irritability and great dependence on others have frequently been identified as "regression" to conduct more appropriate to early stages of psychological development, not appropriate for an adult, and that attempts at securing such dependent satisfactions or expressing hostility should therefore be discouraged This rather moralistic approach ignores the fact that in the postoperative and convalescent period patients are realistically dependent upon others for satisfaction of needs which they themselves are ordinarily able to meet It is not pathological, when threatened, to look to others for support and help Dependence in these circumstances is related more to the feeling of being threatened or of having been rendered helpless, than to sudden decay of character If legitimate dependent needs are not adequately met by medical and nursing personnel, further anxiety can be generated and the patient can be convinced that his needs are not understood Some individuals, usually those who have considerable unconscious guilt for which the illness is partial punishment, may believe themselves legitimately rejected or abandoned, and become seriously depressed

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Cosmetic preoccupations are less a problem with thoracotomy than

with other types of radical surgery. Anxiety and *depression are therefore* less related to these than to the believed or experienced difficulties in performance of the individual's daily life activities. There may be real interference with breathing function. Unfortunately, patients with cancer in one lung may have serious degrees of functional impairment of the other. Lobectomy or pneumonectomy can therefore result in decrease in ventilation sufficient to render them anoxic or dyspneic on very little exertion Even when the remaining lung tissue is healthy, there may be sufficient decrease in the ventilation capacity so that previous activities cannot easily be undertaken The resulting dyspnea may therefore underline or intensify feelings of profound body injury and hypochondriasis.

It has been stated above that a large number of people approach surgery with lively expectations of death or of severe injury. Such expectations can unfortunately become converted immediately postoperatively into the firm belief that irreparable damage has taken place. The body cannot therefore be expected to function as it did before. A surprising number of patients appear to believe that the surgical removal of an organ results in lessening of the total body energy or "resistance" regardless of the true function of the part *The diminution of energy not only necessitates* a corresponding diminution of activities, but also leaves the body vulnerable to recurrent cancer and to other diseases. "I treat my body like a soft-boiled egg liable to break my shell at any moment." "I have lost confidence in my body"

The hypochondriacal reaction can be very disabling. Restrictions of function that it imposes are manifested in all of life's activities. Work restriction appears as a downgrading job shift or decreased productivity at the same job. There is almost always deterioration of earning power. This in turn is reflected in the male patient's status at home. Decreased earning power is frequently associated with a marked loss of self-esteem and esteem from others In contrast, if the patient must *continue to* work at his previous level he may do so only with considerable anxiety, and usually entertains the beliefs that the energy expended at work will result in his catching other diseases or having a recurrence of cancer, and that the demands of his family are driving him to an early grave. The sense of body weakness may herald the onset of "old age" which is frequently dated from a major surgical experience

Social activities are similarly restricted as the patient does not feel himself able to afford the energy. Recreation may confine itself to the television set Sexual activities are interdicted when the sense of weak- [illegible] activity depletes the body of

on the chest. Here a very frightened patient gives up an activity about which he unconsciously feels guilty, in order to preserve his life

The hypochondriacal reaction is rather regularly accompanied by depression, focusing on the need of forgoing many of the activities which were valuable or pleasant to the patient in the past The depression, though severe, is rarely suicidal because the referents of depression are maneuvers which are designed to save the patient's energy and hence his life

Such patients are often accused of malingering, of "goldbricking," or of utilizing the illness for "secondary gains" It does not require skillful questioning to elicit the underlying profound conviction that the body has been irreparably damaged by the disease and its cure The therapy of this postoperative hypochondriasis lies mainly in its prevention, for once it is well established it is one of the most difficult psychiatric states to manage Sometimes, but not always overtly associated with hypochondriasis, are paranoid reactions There is usually covert paranoid thinking manifested in ruminations over the necessity of such extensive treatment

Serious paranoid reactions are often seen postoperatively in those who preoperatively denied the existence of the disease or the necessity for operation These reactions may continue in the postoperative period as attempts to deny the existence of the disease by denying the need of such extensive surgery Paranoid reactions are perhaps more common when sexual or sexualized organs are removed, but can occur with any operation It occurs typically in guilt-ridden individuals, for whom the disease, operation, and organ loss appear as punishment They are filled with self-directed rage, often suicidal in intensity Projection outward of rage and guilt onto malign figures in the environment, often the surgeon, seems to be a life-saving maneuver Nevertheless, individuals with serious paranoid reaction are potentially suicidal As a rule, the better developed the paranoid structure the less the suicidal risk

X-RAY THERAPY

There have been little formal psychiatric studies of reactions of patients to x-ray therapy Clinical experience leads us to believe that here the patient's approach to x-ray therapy is to a great extent determined by his relationship with his doctor If the relationship has been one in which there has been reliance on the physician, referral for x-ray treatment is seen as neither a last-ditch stand nor as an abandonment Only an occasional patient will develop phobic reactions to x-ray machines or intense fear of the mysterious rays Nausea and vomiting rarely prove insuperable psychological barriers to continued x-ray therapy if these

are explained as not infrequent complications of treatment, and as temporary and controllable by medication.

The radiotherapist is perhaps as important an agent for the relief of anxiety as is the alleviation of symptoms by the therapy itself. The patient sees him as in control of mysterious and powerful forces which he can leash and unleash at will, powers that can cure disease and prolong life. The patient must feel sure that the therapist is an expert in his field and so can control potentially damaging forces, and that he also respects the patient as a human being for whose benefit he will utilize these forces.

THE TERMINAL PATIENT

Few patients wish to know that they are going to die; yet the steady deterioration of their physical status makes it necessary for them to handle the evidence of their own mortality. How this is done is a highly individual matter (6). The psychological adaptation to the terminal phase of cancer cannot be subtracted from the sequence of events that have taken place since the beginning of symptoms, or from the totality of the patient's life experience The quality of his relationship to his family, friends, and physician enormously modifies his reaction to his physical deterioration So many factors are operative that it is hard to predict which will control the tone of this experience A calm realistic acceptance of death is perhaps more common in the aged whose ties to life have atrophied and for whom life itself may be uncomfortable, or where it is thought a "good life" has been fulfilled But age itself is no guarantee that death will be calmly accepted.

A number of individuals blandly deny the existence of serious illness at all, and frequently show a very childlike, uncritical faith in the physician This group is perhaps the easiest to manage as long as the mechanism works, and is certainly the most comfortable for the physician A variant of the denying group that is far less comfortable to handle are those whose denial of the threat is less successful and whose excessive demands for attention and relief of symptoms are in reality frantic attempts to bolster the denial. Occasionally the threat of death can be handled only by displacement and obsessive ruminations of what are essentially irrelevant or unimportant matters It is less frightening to worry about something less important than death, moreover, obsessive thinking and little rituals serve the purpose of a magical defense or expiation by which feared injury can be averted, and are closely akin to the magic ritualistic practices of primitives

A certain number of individuals will react to the threat of death by a marked increase in their dependent demands They are frantically

trying to integrate others into their system of defenses to protect them against the ultimate defeat

Disease may fortuitously enter into a profound depressive system and may in fact serve the purpose of a longed-for suicide Such patients may not appear clinically depressed and should not be confused with those who develop agitated depressions when confronted with the threat of death, as these latter are serious suicidal risks

Occasionally, an apathetic depression takes place as a terminal event in the life of a solitary, paranoid personality who in the main has alienated most meaningful relationships Such patients are not comatose, stuporous, or retarded, but are well-oriented and can be aroused They are totally indifferent to the events about them and their own approaching fate The usefulness of this mechanism is apparent.

Frank psychoses are rare. There may be profound retarded or agitated depressions with frank expressions of hopelessness These patients are grave suicidal risks A few exhibit schizophrenic reactions as protective devices, with paranoid outward projection of the threatening forces (it is easier to deal with externalized hostile forces than those which are internalized, such as metastatic cancer) Here again the usefulness of the schizophrenic flattening of affect is apparent This group is, however, potentially suicidal Toxic confusional states are seen postoperatively in metabolic and electrolyte disorders, and hypoxia

Brain metastases from carcinoma of the lung are common These may be manifested only by psychological or behavioral disturbances There may develop the classical "brain tumor" personality, or frank confusion or disorientation suggestive of organic brain syndrome On the other hand, metastases may show themselves only by ideational changes, often paranoid elaborations These may develop rapidly Therefore any serious change in the personality of the patient should be suspected of being secondary to brain metastases

MEDICATION

There seems little reason why the terminal patient should not receive all analgesia necessary for his comfort Nevertheless, it should be remembered that pain has two major aspects that can only be arbitrarily separated The first is the actual amount of pain for which some objective measurement has been attempted in the laboratory, and the other is the meaning of the pain to the individual with its consequent emotional component Anxiety can greatly increase the latter quality of pain and consequently increase the need for analgesics Here these agents are called upon to provide sedation rather than analgesia When anxiety can be lessened, the need for analgesia can be reduced

It is rare to find malingering or hysterical conversion symptoms in the terminal patients Their complaints can usually be accounted for by the real disease present, or by anxiety. That placebos or sterile hypos may modify pain is not proof that no pain exists, for even in normal subjects the suggestive effect of these agents may well serve to raise the threshold of pain The anxiety associated with pain can, of course, be lessened by the evidence that something is being done about the pain, which the administration of a placebo affords.

The roles of Chlorpromazine and Reserpine in the management of the anxieties of cancer patients has not been adequately evaluated at the present time Clinical experience with the usually recommended doses does not show unequivocal benefit in all cases It may well be that the doses are inadequate, as evidence is accumulating that significantly larger doses are needed before the "tranquilizing" effects are seen.

Conflicting reports exist over the influence of these agents on pain Neither is an analgesic and their ability to modify the pain threshold is no greater than placebos (7) Nevertheless, if they can "tranquilize," they may better control the "affective" quality of pain and hence decrease the need of analgesics for sedative purposes

FAMILY

The nature of the relationship between the [illegible] any phase of [illegible] ship before [illegible] spouses has be[illegible] the patient can expect support and sympathy in the preoperative or pretreatment phase with practical help in making arrangements The patient can expect and can accept body nursing care from the spouse when he returns home. He will continue to be loved despite impairment of earning power, and, if the patient is a woman, her failure to perform household tasks as effectively as before will be well tolerated if not expected If advanced cancer develops, the same warmth and support can be expected, as well as suppression of the spouse's own grief with efforts designed to sustain the patient's morale Such unions seem to be based on mutual affection and trust with no serious conflict in economic or sexual matters

A large group of marriages are essentially "façade" marriages, in which the partners are indifferent or ambivalent to one another and expect little from each other Such marriages seem to have been entered into as socioeconomic unions without mutual affection or trust, and little affection or trust develops As a rule the wife is frigid and the husband feels that his legitimate sexual demands have not been met. Frequently the wife feels that her economic security is poor and the husband believes

that the wife is exploitative and grasping Such marriages appear to endure because of social pressures, or "for the children's sake," and often buttressed by the wife's desire for married status or by the husband's guilty acceptance of economic inadequacy as an adequate explanation for failure of the marriage

In this type of marriage the patient can expect little help from the spouse who is usually excluded or excludes himself from planning for treatment or for postoperative care Patients are vehement in protesting their independence of the spouse, their lack of need for care, for the good reason that none would be forthcoming if they should demand it. What care there is is usually symbolic, such as the preparing of certain types of food commonly held to be therapeutic or fit for the invalid stomach

In many marriages the partners are frankly hostile to each other Here again the wife is usually frigid and complains bitterly of her husband's economic or other deficiencies The husband is equally vehement about his wife's frigidity, her greed, and her lack of interest in him No help may be expected from the spouse in any phase of the illness, no nursing help is given, no emotional support is offered, and indeed frank expressions of hostility are the rule During the phase of advanced cancer or the terminal phase the spouse tries to transfer as much responsibility as possible, and to have as little as possible to do with the patient

Occasionally the hostile spouse may simulate the interested spouse in the early pretreatment phase, by forcing the patient into treatment This is not done for the patient's sake but rather to prevent further deterioration of the spouse's own position or the imposition of an unwelcome burden This does not appear to be "reaction formation" in a majority of cases as the hostility continues, and is very frankly expressed

In an occasional case the spouse or family may dramatically over-react When this is not culturally felt to be an appropriate attitude, it represents reaction formation to profound covert hostility to the patient. Evidence of this hostility is rather easy to see.

If the patient has been the strong member of the family about whom it pivots, the other members may need considerable help in readjusting their lives to his invalidism or to his demise Alarming symptoms may precipitate disorganizing panic related less to hostility than to powerful realistic dependency needs In those families where the patient has been a very dominating parent, the children, even though adult, may find it impossible to force on him or even urge him to accept treatment intended for his own good

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FAMILY

The nature of the relationship between the patient and his family during any phase of illness will be directly related to the nature of their relationship before illness (8). If, on the whole, the relationship between the spouses has been warm, then the patient can expect support and sympathy in the preoperative or pretreatment phase with practical help in making arrangements. The patient can expect and can accept body nursing care from the spouse when he returns home. He will continue to be loved despite impairment of earning power, and, if the patient is a woman, her failure to perform household tasks as effectively as before will be well tolerated if not expected. If advanced cancer develops, the same warmth and support can be expected, as well as suppression of the spouse's own grief with efforts designed to sustain the patient's morale. Such unions seem to be based on mutual affection and trust with no serious conflict in economic or sexual matters.

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If terminal care is to be given in the home, the family may need considerable support in dealing with the steady deterioration of the patient The family should be thoroughly aware of what symptoms or events to expect They should not feel that the physician is inaccessible for

consultations that serve as reassurance, if for no other purpose. Family members may feel personally responsible for the health and welfare of the patient and consequently symptoms which seem very minor to the physician may appear a major threat to them because of the implication that they are neglecting their duties to the patient. If there has been ambivalence towards the patient, the implication may be particularly difficult to endure.

Even in the successfully treated patient there are numerous problems to be met as he reintegrates himself with family life. His family is aware that he has lost a lung or a large section of a lung. He may well be regarded as more of an invalid than he is, and the family's own hypochondriacal notions of body injury may be projected on the patient with consequent overprotection or troublesome restrictions. The patient himself may express hostility or depression by querulousness and irritability which can seriously disrupt family relationships

The spouse is the preferred source of nursing care. When one is not available, adult children must reluctantly be relied on. The impact of nursing a sick parent on these children may be severe if it is protracted There may be considerable deterioration in the child's own marriage. The children, especially the daughters, seriously resent the restriction of their freedom, which may be described as "living in a nunnery." The onset of their own "old age" is dated from the time the parent came under their care. Many children, especially those of old men who are invalided, wish that the parent had died at the time of operation even though he is apparently cured of disease. Old women who have been cured of cancer and who are invalided to some extent may be better tolerated because of their functions as baby-sitters or auxiliary household help The destruction of the family pattern may extend into the third generation and instances have been demonstrated of truancy and running away from home in grandchildren of patients who are being taken care of by their married children.

The patient is quite aware of the disruption he is causing. The very high value put in our civilization on self-sufficiency and helping others but not relying on others makes it most difficult to accept a dependent role The restoration of a measure of independence or self-sufficiency, even if largely symbolic, is a *sine qua non* for the rehabilitation of these patients

Family anxieties may well be aroused by the possibility of "catching" cancer. Chronic cough has traditionally been associated with communicable disease and the patient thought to be emitting cancer cells or other noxious emanations. There are instances where patients have been virtually isolated from other members of the household, even to their food

being served on plates reserved for them and their laundry isolated. They are treated as highly infectious beings

In general it should be stated that where relationships before the illness have been good they usually continue to be good and prove assets to the patient. When the relations within the family have been poor before illness they usually deteriorate and offer little in the way of positive support, or may be frankly detrimental Satisfactory solution of these problems may be beyond human ingenuity Nevertheless, the physician can secure considerable help in these areas from social workers or family agencies whose training has accustomed them to working constructively with family groups

THE DOCTOR-PATIENT RELATIONSHIP

Fortunately most patients do not present serious problems in management Nevertheless, almost all patients with serious disease whose treatment implies a profound threat to the integrity of the body and its function, do have emotional problems Some of these may result in unnecessary restriction of function or unnecessary unhappiness For the solution of these problems the patient's first choice, and indeed in most instances the most effective person, is his own physician or surgeon. The psychiatrist can be useful in the management of psychiatric emergencies He can also aid in evaluating the patient and guiding the surgeon or physician

The therapist, be he radiologist, surgeon, or physician, of a case of cancer of the lung, or of cancer or serious illness of any sort, is involved in as brisk a "transference neurosis" as any psychiatrist The physician may be seen unconsciously or at the margin of awareness as having complete power over the course of the disease In some disturbed individuals he is even seen as having the power to cause the disease He becomes erected into an all-powerful parental figure capable of reward or punishment, capable of protecting or abandoning the patient Consequently, if he can be seen as a warm and supportive figure, the threatening aspect of the all-powerful parent is correspondingly reduced and the patient can trust the physician and talk over his preoccupations and ruminations without fear of hostility or rejection Whenever the physician remains cold and distant, or cannot accept his patient's legitimate dependent needs, the patient is deprived of a powerful defense against anxiety and undesirable posttherapeutic reactions If the patient is lucky, he can convince himself that the physician is a trustworthy figure by virtue of the fame of the institution with which the physician is connected, or because of the physician's own great eminence which the patient usually magnifies

These reassurances remain at best far less effective than warm personal rapport.

The physician should seek out and correct physiologic misconceptions, as these are the bases for the patient's later actions and activities. Such notions include the belief that the loss of a rib has seriously damaged the subjacent thoracic structures or the heart, or that the thoracic wall is now weakened, or that the loss of part of the lung has seriously weakened the entire body apart from the obvious limitation that is based on respiratory function, or that the surgical experience itself apart from what organs have been removed permanently depleted the body of valuable energy

The physician who undertakes the care of the cancer patient has assumed an onerous personal burden. The surgeon's responsibility cannot stop when his surgical work is finished, nor the radiologist's when he has outlined the areas for treatment and delivered the patient to the technicians The patient very much needs to be treated as a human being and not simply as the bearer of an interesting lesion. He needs desperately to relate to these powerful figures whom he has enlisted in his defense against the forces of darkness, and of whose benignity and helpfulness and interest in him he needs constant reassurance

The physician should not allow his own guilt for being unable to do more than give palliation, tempt him to avoid or to abandon the patient Avoidance or abandonment will be interpreted as evidence of hopelessness, or of unworthiness which may reinforce a sense of guilt Moreover, the physician should not neglect the family, for it is with them that the emotional problems may be most severe

If a patient has been sent to treatment centers, the referring physician may not be kept fully informed of progress of treatment of the disease or future plans Consequently, when the patient is sent home the referring physician may be frightened by the physiological or therapeutic problems presented, or repelled that he is called in merely to give opiates. If there has been a good rapport between referring physician and treatment center, the transition of the patient from the hospital to his home and his physician's care is greatly facilitated. This in turn makes the family's problem easier, for if rapport has not existed, the family physician frequently makes his lack of understanding of the problem only too clear to the family This in turn increases their feeling of being abandoned with a sick person for whom they can do little.

INFORMATION

There is a recurrent question—should the doctor tell the patient he has cancer? In this form this question cannot be answered because it pre-

supposes a standard doctor, a standard patient, and a standard cancer, none of which exists Probably most patients can withstand the knowledge that they have cancer without total disintegration, but it is never a pleasant experience and serious psychiatric difficulties have been precipitated by it Information about a skin cancer is considerably easier to give and to receive than that about cancer of the internal organs, such as cancer of the lung Moreover, doctors differ greatly in their abilities to handle anxieties, to practice the "art of medicine"

Our aim is not to give each patient an education in cancer but to permit him to co-operate with therapy with a minimum of anxiety. The physician must remember that the capacity of a patient to integrate threatening information may be limited When he meets a patient who denies wholly or in part the existence of his illness, unduly minimizes symptoms, or refuses to draw a reasonable inference about his illness from the evidence around him, then the physician should realize that he may well be dealing with a person whose ignorance is strongly motivated and purposeful Such "ignorance" had better be respected because serious disorganization may be precipitated if unwanted knowledge is forced on the patient

The "how" of telling is just as important as what is told If a good relationship exists between the physician and patient, specific information becomes less important and unpleasant information easier to integrate The patient is less interested in an academic discussion than in being assured that the physician, his ally in times of threat, can manage the disease The patient cares less about what ails him than that he is going to get well

As a matter of fact, no physician fully lies to the patient and none wholly tells the truth Lying to the patient entails the offering of a course of action consistent with the lie One would therefore have to tell the patient with operable cancer of the breast that she needed no operation * One would have to tell the patient with operable cancer of the rectum that he needed no operation We would have to tell the patient with operable cancer of the lung that no surgery was indicated On the other hand, even the staunchest advocates of truth do not tell patients the exact percentage of chance they have for survival, or describe the routes of spread or explain that in all probability the cancer has already reached inaccessible lymph nodes, that it will ultimately metastasize to the liver and possibly to the brain, or that, interestingly enough, carcinoma of the bronchus may occasionally involve the adrenals and simulate Addison's disease A medical school lecture to the patient of

* Not infrequently a patient will accept the statement that he or she has a benign lesion that must be treated surgically, despite the true malignant nature of the lesion —ED

such a nature would cause the patient to leave by the nearest aperture, be it door or window. It should be noted in passing that physicians regularly overestimate the power of their colleagues to absorb damaging information when they are patients. The physician, who might have gone into medicine in order to master his own hypochondriasis, may be no more able to integrate the anxiety of threatening death than any other human being.

The problem of what to tell the patient and how the patient uses this information can never be predicted in advance by formula. How, when, and how much information is imparted to a given patient is always a matter of the most exquisite clinical judgment of the physician Such discretion is the distinguishing characteristic of the art of medicine

TOBACCO SMOKING

The physician must sometimes persuade his patient not to smoke. Most patients with lung cancer will stop smoking spontaneously and perhaps after cancer has developed it is of academic interest whether the patient stops or not

The physician's attitude toward smoking will inevitably be affected by whether he himself smokes or whether he has ever stopped smoking. There are few areas of medicine more subject to firm opinion and less fact than in the discussion of why people smoke or why they continue to smoke. It should be remembered that why people start to smoke and why people continue to smoke are probably two different things The individual first begins to smoke, usually in his late teens or early twenties, as a result of social pressures It is conceived of as fashionable or as adult. Among boys, cigarette smoking is frequently a symbol of masculinity. To the young adolescent, sure of neither his masculinity nor his adulthood, the assumption of adult masculine habits can be very reassuring, so reassuring that much discomfort during the development of tolerance to nicotine can be endured.

Once tolerance to nicotine has been established, other factors enter in Conventional psychoanalytic literature describes the "oral" infantile pleasure from sucking There is also a discharge of tensions in the activities associated with lighting and manipulating a cigarette. There is the pleasure derived from the taste and a certain pleasure derived from the irritation of the trachea and bronchi by smoke, perhaps derived from the desire to "incorporate" something or someone. There are numerous cues which suggest smoking, such as certain types of food, especially coffee or alcoholic drinks, or certain situations, for example intermissions at the theater Tobacco lessens the demands of hunger and fatigue by inhibiting gastric motility and perhaps by raising blood sugar. The

tobacco smoker has with him throughout the day numerous reminders to smoke, both from within and from without

There can be little doubt that smoking represents "addiction," albeit to a mild degree. There is a recognized habituation to nicotine and a tolerance thereto Sudden withdrawal results in a well-recognized set of symptoms lethargy, irritability, restlessness, craving, and bradycardia These symptoms, plus the ever-present internal and external cues to smoke, make it most difficult for the poorly motivated "addict" to stop smoking In addition, the almost invariable and widely known weight gain which takes place following cessation of smoking is a potent motive for many people to continue smoking

CONCLUSION

Any cancer patient is a permanent patient even when his cancer is in reality cured. There is usually some serious change in body form or function which may require considerable medical supervision There are numerous family problems which may be brought to the physician *There is always the fear of recurrence which makes symptoms of banal* illnesses threatening and which drives the survivor to seek reassurance from his doctor

Unfortunately it is only too rare that a patient with lung cancer is cured and can be dismissed. He must always know that his physician is available to him for guidance, help, or reassurance so that physical palliation may be accompanied by mental palliation and that the time saved can be useful and happy for him and others

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19

Benign Tumors of the Lung; Benign and Malignant Tumors of the Trachea; Tumors of the Pleura

Herbert C. Maier

BENIGN TUMORS OF THE LUNG

Although this book is primarily concerned with all the various aspects of malignant tumors of the lungs, a brief discussion of benign tumors is herewith included in order to clarify the differential diagnostic features. These benign neoplasms may be considered in two groups according to the site of the growth. There are (1) *benign endobronchial tumors*, and (2) *circumscribed benign tumors of the pulmonary parenchyma*. It should be noted that the controversial bronchial adenoma and cylindroma are not considered with the benign tumors but have been discussed as a separate group among the malignant growths. Tumors of the pleura, both benign and malignant, are considered in a separate section of this chapter.

The incidence of benign tumors of the bronchi and pulmonary parenchyma is somewhat difficult to determine because certain tiny growths can readily be overlooked at an autopsy done in a routine manner. Moreover, many of these tumors, when small, cannot be identified on roentgenograms of the chest. If consideration is limited to those cases in which the tumor attains some clinical significance, the benign neoplasms may perhaps constitute 1 to 2 per cent of all primary tumors of the lungs. The incidence of 3 to 5 per cent quoted in the literature some years ago now seems too high because of the great increase in the occurrence of cancers of the lung.

Benign Endobronchial Tumors

Benign tumors which arise from the bronchial wall and project into the lumen of the bronchus without significant extension into the adjacent

extrabronchial structures are very rare, if inflammatory granulomatous lesions are excluded from consideration. A benign tumor, derived from one or more of the component structures of the bronchus, may be a papilloma, polyp, fibroma, lipoma, chondroma, leiomyoma, osteoma, or lymphoma. Adenomas should be considered as a separate group because of their tendency to extrabronchial invasion, although occasionally a bronchial adenoma may be almost entirely an endobronchial lesion. The tumors cause symptoms by encroachment on the bronchial lumen. If the tumor is small and does not obstruct the bronchus to any marked degree, symptoms may be absent. A dry cough may be one of the earliest complaints. When the tumor arises in one of the larger branches of the bronchial tree, wheezing may be noted if the bronchial lumen is partly obstructed. Many patients with these signs and symptoms are erroneously diagnosed as having asthma. A roentgenogram of the chest may be negative. Fluoroscopy may sometimes indicate partial bronchial obstruction by demonstrating interference with the emptying of air from a portion of the lung. The involved lobe remains more radiolucent on full expiration than the normal portions of the lung, which can deflate to a normal degree. If the main bronchus to an entire lung is partially obstructed, fluoroscopy may demonstrate displacement of the mediastinum toward the contralateral side on expiration, and failure of the diaphragm, on the side of the bronchial obstruction, to ascend normally with expiration. The same findings may be demonstrated by roentgenograms of the chest taken in deep inspiration and full expiration. If the tumor obstructs only a small bronchus, these findings may be absent. In some cases the tumor casts a shadow on the routine roentgenogram of the chest or is seen on tomographic films. Bronchoscopy is the chief diagnostic method for endobronchial tumors of the larger bronchi, and should be performed in cases of localized wheezing even when the radiographic findings are negative. As the bronchial obstruction becomes more complete, atelectasis, usually with secondary suppuration, supervenes.

Frequently a diagnosis of endobronchial tumor is not made until after secondary suppuration has occurred. The clinical picture of a pneumonia is then the presenting feature. A pneumonitis distal to a bronchial obstruction may cause bronchiectasis and even abscess formation. Such a pneumonitis usually does not respond dramatically to antibiotics, although considerable temporary clinical improvement may follow their use. The clinical benefit may be more marked than the roentgen evidence of clearing of the pulmonary infiltration. The omission of repeated roentgenograms during the course of a pneumonitis is often responsible for the failure to recognize that the pneumonitis is chronic because it is secondary to a bronchial lesion. Early diagnostic bronchos-

copy is indicated in any case in which there is a suspicion that the pulmonary infection might be secondary to bronchial obstruction.

The treatment of benign endobronchial tumors depends on the location of the growth, its pathologic characteristics, and the presence or absence of significant distal secondary suppuration. If a diagnosis is made before significant infection has developed distal to the site of bronchial obstruction, local endoscopic removal of the tumor may result in cure. Because it may be difficult to determine bronchoscopically how far the base of the growth extends into the bronchial wall, it is usually not possible to be certain whether the lesion has been completely removed. For this reason transthoracic resection of the growth by bronchotomy and plastic repair of the bronchus may be preferable, especially if there is any doubt about the pathologic characteristics of the neoplasm. If the endobronchial tumor is located in one of the smaller branch bronchi not visible bronchoscopically, and no tissue for biopsy can be obtained, a definite diagnosis usually cannot be made preoperatively. In such cases, *resection of the involved portion of the lung is indicated. Even in those* cases in which the tumor can be removed bronchoscopically, pulmonary suppuration secondary to the bronchial obstruction may have caused sufficient bronchiectasis to require removal of the involved portion of the lung. *Lobectomy or pneumonectomy, depending on the location of the* tumor, is then indicated. The radical operation should be postponed if the patient is febrile or has signs of toxemia from infection, because in such an instance partial removal of the tumor bronchoscopically will cause partial subsidence of the infection and will render the patient a far safer candidate for later radical surgery.

Circumscribed Benign Tumors of the Pulmonary Parenchyma

Circumscribed benign tumors unassociated with a bronchus and located in the pulmonary parenchyma are rare. Included in this group are chondromatous hamartoma, fibroma, leiomyoma, lymphocytoma, neurofibroma, xanthoma, and plasmocytoma. *There is nothing characteristic* in the clinical picture. The exact diagnosis is often not established until the tumor has been removed surgically. *Since tumors in the pulmonary* parenchyma rarely obstruct any large bronchus, the symptoms of bronchial obstruction and secondary suppuration are usually absent. If the tumor is small, there may be no symptoms and the lesion may be a chance finding on a routine chest roentgenogram or at autopsy. There may be a cough which is often nonproductive. Hemoptysis and chest pain are infrequent. Definite differentiation of benign tumors of the pulmonary parenchyma from bronchogenic carcinoma is usually not possible, as a carcinoma of the lung may be just as sharply circumscribed on the roent-

genogram as a benign tumor. Lobectomy, either partial or total, will usually suffice

Chondromatous hamartomas are the most common of the circumscribed benign tumors of the pulmonary parenchyma (Fig 153). The term hamartoma is derived from a Greek word which means "to err."

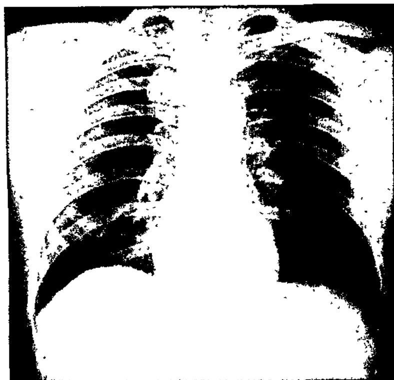


Fig 153 Asymptomatic tumor mass in right upper lobe of a 35-year-old male Local surgical excision was performed for this chondromatous hamartoma

The tumor is due to a malformation in which there is an abnormal mixing of various normal components of the organ Since these intrapulmonary hamartomas consist largely of cartilage, they have usually been called chondromas The presence of other structures within the tumor makes the term chondroma unsatisfactory The characteristic chondromatous hamartoma of the lung is a solid tumor which consists of benign mesodermal and epithelial elements Among the cartilage one finds cystlike spaces lined by columnar epithelium. Smooth muscle, mucous glands, and fat are also usually present The connective tissue may be myxoma-

tous in type Bone is occasionally present. In contrast to true chondromas, which arise from the bronchial cartilages, the hamartoma is usually located near the periphery of the lung, where no large bronchi are present In some instances the tumor may be directly beneath the visceral pleura, or may even project above the pulmonary surface The adjacent lung tissue is usually normal.

A correct diagnosis is rarely made preoperatively because the roentgen appearance simulates that of other pulmonary lesions. At operation it is important for the surgeon to recognize the true nature of the lesion, so that only the involved portion of the lung is removed. Local excision or partial lobectomy is usually adequate Malignant degeneration is apparently a very rare occurrence.

The benign tumors of the pulmonary parenchyma derived from muscle and nerve cells are very rare. Most of the reports of these tumors have appeared recently because such growths were often classified as fibromas in the past. Yet even the older literature contains very few reports of fibromas within the lung that were not endobronchial.

Lymphocytomas and plasmocytomas are very uncommon. Differentiation between benign and malignant forms of these tumors is uncertain Moreover, in some cases it has thus far been impossible to be certain whether certain tumefactions in the lung are of inflammatory or neoplastic origin Fever and other systemic reactions may be noted in some of these patients Morphologically the tumors may simulate xanthomas, fibromas, and plasma cell tumors Further experience is necessary to solve this question

BENIGN AND MALIGNANT TUMORS OF THE TRACHEA

Primary neoplasms of the trachea are rare. Primary carcinoma of the trachea, in sharp contrast with carcinoma of the bronchus, continues to be a rare lesion Ellman and Whittaker collected a total of 507 tumors of the trachea from the literature up until the end of 1945. These tumors were divided as follows: benign tumors, 253 cases, carcinomata, 187 cases; other malignant tumors, 38 cases, and tumors of doubtful histology, 29 cases The number of benign tumors in this series is proportionately higher than that of some other reports because almost a third of the benign tumors were cases of tracheopathia osteoplastica, which describes the condition of multiple exostoses of the trachea, many might not consider this to be a truly tracheal tumor *Papillomas* constituted the next most common type of benign tumor of the trachea Here too a sharp line of distinction between a hyperplastic proliferation in response to chronic inflammation and true neoplasia may be difficult in certain in-

stances About 15 per cent of the benign tumors were fibromas and 10 per cent were intratracheal goiters

Although that report, like many others, lists the adenomas and mixed tumors of the salivary gland type including cylindromas among the benign growths, it would seem preferable to list these cases among the malignant tumors, bearing in mind their slower growth pattern Among the cases listed as carcinomata, an analysis revealed the following distribution of histologic types adenocarcinomata, 47 per cent, squamous cell carcinomata, 41 per cent, and basal cell carcinoma, 12 per cent.

The symptomatology of both benign and malignant tumors of the trachea may be considered together because in the earlier stages when diagnosis is desirable, the symptomatology of the malignant growths may not differ from that of the benign tumors Tickling of the throat with an irritating dry cough is often the first complaint Wheezing of a stridorous character may be noted as the growth increases in size and encroaches on the tracheal lumen All too often such wheezing is erroneously interpreted as a sign of bronchial asthma Dyspnea appears as the tracheal obstruction increases and may ultimately become a very prominent symptom with characteristic tracheal stridor The dyspnea may be



Fig 154A and B Inspiratory and expiratory roentgenograms of a 34 year-old woman with history of brassy cough productive of blood tinged sputum, and weight loss Routine film in inspiration fails to demonstrate any abnormality whereas the film in expiration shows displacement of the mediastinum to the right due to obstructive emphysema of the left lung Bronchoscopy revealed a carcinoma of the lower trachea predominantly involving the left side



Fig 155 Lateral roentgenogram of patient with carcinoma of the lower trachea which encroached upon the esophagus, causing some dysphagia in addition to dyspnea

both inspiratory and expiratory in type and at times is influenced by the patient's position Malignant growths of the trachea may invade through the wall and cause symptoms such as dysphagia from esophageal invasion, or hoarseness and euphonia from involvement of the nerve pathways adjacent to the trachea Loss of weight may occur with the malignant tumors

Physical examination may reveal prolongation of inspiration or expiration, or both, over the lungs bilaterally. Sometimes when the growth is located in the lower trachea on one side, the auscultatory changes may be more pronounced on one side or limited to one lung With malignant tumors, metastases might be palpated in the cervical region

Routine roentgenograms of the chest are often negative and this fact may lead to undue delay in establishing a correct diagnosis Careful fluoroscopy may be more informative in cases of lower tracheal tumors that encroach on one main bronchus more than the other, in such instances mediastinal shift with respiration may be noted (Fig. 154 A and B). Tomographs of the trachea may be helpful Bronchoscopy is the principal means by which the diagnosis is established The type of tumor may be determined by bronchoscopic biopsy. Roentgen examination of the esophagus is desirable in order to determine whether the adjacent esophagus is also involved (Fig 155) Endoscopic inspection of the esophagus is indicated in malignant cases In some cases of carcinoma it may be difficult to establish whether the growth arose in the trachea or esophagus Secondary involvement of the trachea by carcinoma of the upper esophagus is not uncommon When a neoplasm has produced a tracheoesophageal fistula, the carcinoma usually is primary in the esophagus

Treatment of primary tumors of the trachea depends on the nature and extent of the growth. Benign tumors may be treated by endoscopic removal or surgical resection, with plastic repair of the tracheal defect Most malignant neoplasms of the trachea are treated by radiation therapy preferably with supervoltage In less extensive carcinomas of the trachea, and especially with localized cylindromas, surgical excision with tracheal reconstruction may be the treatment of choice

TUMORS OF THE PLEURA

The literature on tumors of the pleura is quite contradictory because it is often difficult to ascertain that a particular neoplasm arose from the pleura rather than from the underlying pulmonary tissue Moreover, there are many tumors of the chest wall, mediastinum, and diaphragm recorded in the literature as pleural tumors because they projected exten-

sively into the pleural space, although the overlying parietal pleura was merely evaginated into the pleural cavity. It would seem best to reserve the designation of "tumor of the pleura" for those cases in which the main bulk of the lesion lies within the pleural cavity and the neoplasm shows certain pathologic characteristics which suggest origin from one of the component cellular elements of the pleura. Actually clinical experience has demonstrated that a rather distinctive group of tumors fulfilling these requirements can be recognized.

Although primary tumors of the pleura are uncommon, such neoplasms are now being encountered more frequently because of the increased use of chest radiography and surgical exploration of the thorax. The clinical, roentgen, and pathologic characteristics of these tumors vary, but increased experience with such lesions points to certain features which should suggest their consideration in differential diagnosis.

Primary pleural tumors may conveniently be divided into localized and diffuse types. Usually the clinician thinks of the diffuse lesion, namely the malignant diffuse mesothelioma, when the subject of primary neoplasms of the pleura is considered. Yet the localized type of tumor is not as rare as previously considered, and its recognition is, in a sense, of greater clinical value because of its more successful therapeutic management.

At this point it may be well to recall that the pleura anatomically consists of a layer of connective tissue covered by a layer of mesothelial cells. Within the connective tissue are smooth muscle, fat, blood vessels, lymphatics, and nerve fibers. Tumors could arise from any of these components of the pleura.

Stout has recently shown with the aid of tissue cultures that in all probability the localized pleural tumors which have been reported as fibroma, fibrosarcoma, myxosarcoma, leiomyosarcoma, and endothelial sarcoma are actually all variations of the same neoplasm, namely the solitary mesothelioma of the pleura. The tissue culture studies demonstrated that a pleural tumor composed of cells with the microscopic appearance of fibroblasts imitated the behavior of mesothelial cells in vitro. Thus tumors of mesothelial origin may present the microscopic appearance of a fibroma or fibrosarcoma. Moreover, some of these so-called fibromas showed areas with mesothelial lined spaces such as are not seen in a true fibroma. Many of the previously reported fibrosarcomas showed no metastases even though the tumor had been present many years and had attained huge size. Therefore, it was often uncertain whether the growth was [illegible] ...ant. In retr[illegible] ...ould seem probable that some of the [illegible] ...e actually [illegible] it should be emphasized that the his[illegible] ...n betw[illegible] ...nd malignant may be uncertain.

Pleural tumors are most frequently attached to the visceral pleura. Often the greater part of the mass is free in the pleural cavity with both visceral and parietal attachments Primary pleural tumors occur in all decades Malignant pleural mesothelioma is not uncommon under 20 years of age in comparison to the extreme rarity of malignant pulmonary tumors in that age group

Most localized pleural mesotheliomas do not produced significant pulmonary symptoms Chest pain is usually present only in the malignant



Fig 156 (A) Asymptomatic tumor in the left midlung field discovered in a 50-year-old woman The lateral film (B) shows the rounded tumor in the midchest superimposed on the hilar shadow The preoperative difficulty in deciding which lobe was the site of the tumor was explained at operation which revealed the mass to be in the interlobar fissure, pedunculated from the upper lobe without pleural adhesions Microscopically this was a typical benign mesothelioma Patient well ten years later

mesotheliomas The benign mesothelioma usually appears as a rounded mass of greatly varying size Points which may aid in possibly distinguishing the localized benign pleural mesothelioma from intrapulmonary tumors are 1) location of tumor corresponds to the site of an interlobar fissure or periphery of lung, 2) symptoms are usually absent until the tumor attains large size in contrast to many bronchogenic neoplasms, and 3) pulmonary osteo-arthropathy of long duration is not uncommon especially if the tumor is large and vascular

A positive clinical diagnosis of pleural mesothelioma preoperatively is nevertheless very difficult The treatment of benign mesotheliomas consists of surgical excision of the tumor with a small portion of the lung at the site or sites of attachment, unless the tumor involves a sufficient area of the pleura to require a partial pulmonary resection (Fig 156)

The diffuse malignant type of pleural mesothelioma often simulates a

pleural effusion Fever may be present. Cough and sputum are not unusual Hemoptysis occasionally is present The *roentgen findings* are usually those of pleural effusion, sometimes encapsulated (Fig. 157). Thoracentesis yields bloody fluid *in varying quantity.* The diagnosis may be established by microscopic examination of this fluid Too often the material obtained is not sent to the laboratory because it is assumed



Fig 157A and B Roentgenograms of a 12-year-old boy with a history of chest pain, coughing, and slight fever Roentgen appearance typical of a large encapsulated pleural effusion but needle aspiration yielded only a few drops of blood which on microscopic examination showed malignant tumor cells Pleuropneumonectomy performed. Patient died of recurrence without distant metastasis two years later

to be frank blood. Thoracotomy is indicated but the lesion may be inoperable Radiation therapy may give prolonged palliation in some cases

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20

The Outlook for Cancer

Cornelius P. Rhoads

It is perilous indeed to prognosticate the future, particularly if the view taken involves to any degree the personal bias of the observer. The risk is taken, however, in the particular instance of this communication, with full knowledge of the peril, wholly in the belief that its presence may at worst be useful in arousing discussion, and at best aid in influencing the course of future cancer work.

It seems to this observer that the accepted consideration of the cancer problem, and the approach to its solution, has become overcomplex and somewhat removed from reality Actually, as all would agree, were the question raised, we are striving for the better prevention and cure of cancer in man To achieve these two desirable ends, very substantial sums are contributed annually by generous, public-spirited citizens These funds are expended upon the advice of groups of individuals of the greatest integrity, highest motives, and completely established general scientific competence

The members of these expending, executive groups, created with great care over a period of years, are selected upon two assumptions, neither of which perhaps is really justified by the facts The first assumption is that the masters of extirpative treatment of cancer (by surgery or irradiation) and the experts in the recognition of cancer on morphologic grounds are best qualified to seek its cure and prevention. Even an individual with the best intentions, the sturdiest character, and the broadest vision finds it hard—*after years of labor expended in perfecting a technique*—*to give* over the planning function to another individual with an entirely different background and training

Hence we hear deprecatory comments concerning the efforts to achieve control of cancer by chemical means. Since such control could not under presently comprehensible circumstances decrease, or even *threaten* to decrease surgical or radiologic therapy, one can only view as dis-

tinctly unjustified the current concern of surgeons, radiologists, and pathologists Such deprecatory comments are unfortunate and handicap the effort to seek new methods by limiting the investigators to those individuals in medicine who are prepared to face the opposition of the distinguished masters of the techniques already entrenched as useful in present-day cancer control

The second assumption, believed by this writer to be erroneous, is that sufficient basic information is not yet available to justify an intensive program designed to achieve new means for the cure and prevention of presently uncontrollable types of cancer In years gone by this was correct and led to the use of a very large part of the cancer funds—both public and private—to support and increase the general scientific activity of the country As a consequence, a substantial share of the support of natural science departments in the American universities is derived from cancer funds New personnel were taken on, new activities instituted, and new responsibilities assumed The work is good, and generally valuable To discontinue it would be incredible, a dangerous return to the inadequate levels of investigative work of a previous and obsolete decade Yet to continue at the current level of support without adequate new funds being made available deters the development of new activities indicated by the progress already made It is tantamount to eternal prospecting and never putting down a mine shaft to the ore deposits found.

The question then becomes one of whether or not the vast general effort of the past decade has brought in the needed basic information to justify a new, developmental program in which the advantages gained would be vigorously exploited and new discoveries would be developed into practically applicable procedures All evidence would indicate that such a developmental program is in order

What, then, are the facts? They appear—and probably are—as follows

1 Cancer need no longer be regarded as a "riddle" or a "mystery," those long-outmoded cliches. We see cancer now and expect to see it even more clearly in the future as just another example of Darwinism, of the mutability of cellular species and the survival of the fittest for the environment in which it finds itself. Clearly then the problem of cancer cure becomes one of destroying every cancer cell or permanently restraining their growth The problem of prevention becomes one of defining the biochemical circumstances inducing the mutation (which results in the neoplastic cell) and the biochemical environment which permits the growth of the cancer cell at a rate exceeding that of its normal relatives and parents

2 From the work of Brown and his colleagues (1) there is a new principle which offers a clear, logical, and effective approach to the selec

tive destruction of the neoplastic cell without injury to its normal relatives. This principle is called "the heterogeneity of nucleic acid metabolism" This term, really not so ponderous as it sounds, is simple indeed but sufficiently basic to open to investigation entirely new areas of biology, pharmacology, and experimental therapeutics Succinctly expressed, it means that the composition—and so the metabolism—of nucleic acid, the reproductive unit and control board of all biologic units, is specific for each cell type and very probably specific for the various stages of development and differentiation within those types. In other words, each *kind of cell has its own chemical requirements for the components used* in the repair of its controlling reproductive structure.

3. The possibility of selective destruction of neoplastic as compared with normal cells, *growing at exactly the same rate in exactly the same* environment, has now been unequivocally demonstrated. The proof of this basic and somewhat revolutionary principle has come out of studies by Stock, Biesele, Philips, Clarke, Sugiura, and their associates (2) This possibility is, of course, fundamental to any program of chemotherapy and is one vainly sought by research workers of former years. Even though this principle has been only slowly accepted and still is not *generally recognized as basic, its implications are important, indeed, perhaps they are revolutionary.* It conceivably means that we do not need to seek eternally for some secret as "mysterious as the nature of life itself," but rather can apply *principles and procedures* amply proven to be effective in eliminating other forms of invading and destructive cells This can be done easily and effectively for bacteria, fungi, and protozoa without actually knowing all about the nature of life, and it is now likely that it also can be done for cancer cells Indeed, it has already been accomplished for certain types of transplanted cancer in experimental animals

4 *Human cancer is now available for test, cultivated in the test tube,* in the embryonated fowl egg, and in suitably treated experimental animals. The importance to future work of this development can scarcely be overestimated, although it is little appreciated at this time. Every known principle, laboriously worked out and painstakingly proven, indicates that the control of cancer or any other invading cell depends upon specific susceptibility to injury of the unit of which control is desired. An essential corollary is *that a chemical or combination of chemicals capable* of poisoning one cell type (for example, the malaria parasites) is most unlikely to affect adversely even closely related units Examples of this extraordinary specificity of susceptibility are found throughout the field of experimental and applied therapeutics Exceptions to it are rare indeed

Manifestly, then, the intensive work on cancer therapeusis of recent years, using mouse cancer as a test object, should have yielded cures

specific for that cancer as the form most tested These should be of little use against other forms in mice or against cancer in man Exactly this has occurred

The use of mouse Sarcoma 180 in an extensive screening program in our laboratories has given us a variety of agents capable of restraining that neoplasm Some are actually effective in its cure The result should be recognized as proof of the correctness of the program undertaken, as proof that with suitable planning, staffing, and procedure a cure can be found for the type of cancer used in the experiments. The failure of this program on mouse cancer to yield means for the regular cure or restraint of human disease is paradoxically a real endorsement of the program and an encouragement for the future. It proves, finally and unequivocally, the specificity of antimetabolite action for cancer. It is exactly this specificity which has been doubted in the past, a doubt which has effectively blocked for fifty years serious effort to control cancer with chemicals Its established existence must be taken as justification for an intensive program of future work

The availability, at last, of human cancer for test, modifies still further the total scientific picture toward the favorable side of cancer control Since the use of transplantable mouse sarcoma has given us the means for its control and cure, the newly transplantable forms of various common types of human neoplasms can be expected to do as much for cancer in man

At the moment cancer arising in the human lung, cervix, connective tissue, striated muscle, parotid gland, and oral mucosa is available in mass production in glass, in animals, and on the chorioallantoic membrane of the fertile embryonated egg of the fowl Over one pound of this tissue is being harvested weekly in our laboratories alone It is known to be still human cancer, since it grows on back-transplantation to the original human donor in exactly the form of the original deposit. It has retained for over two years of artificial cultivation the human morphology of its chromosomes, and its human protein, as demonstrated by immunologic means It clearly is human neoplastic tissue capable of growth on essentially any scale desired, and usable for practically any type of biological or biochemical study

We can foresee in the future the gradual replacement of mouse, rat, and fowl tumors now employed in cancer research by cultivated human neoplasms. Clearly, if this is not done, the results achieved in years to *come, although of great interest, will be almost surely not* applicable to our goal—the cure and prevention of cancer in man If done with care on an adequate scale by competent and thoughtful people of various disciplines integrated in a common purpose very important progress toward cancer cure is possible.

In searching for means of cancer cure, the cultures of human cancer are useful in two ways

First, they permit accurate determinations, by the use of atomically labeled metabolic precursors, of the chemical uptake patterns of various types of cancer as compared with similar and dissimilar animal and cancer cells. Furthermore, by determinations of mitotic rates, or by other methods, these patterns can be corrected for the rates of growth of the tissue under investigation Preliminary observations of this type have already been made in our group and by affiliated laboratories. *Highly suggestive and important data have already been obtained. They indicate* that neoplastic tissue differs in substantial degree in its anabolic pattern from any normal tissue so far tested Furthermore, they suggest that each kind of neoplasm may, as predicted, have certain specific, inherited, and comparatively fixed metabolic characteristics.

The results so far—rough, fragmentary, and preliminary as they are—encourage us to believe that in years to come, by a preliminary trial of an implant on the cancer of a particular patient, it may be possible to run a conclusive test This would involve offering the implant a standard series of isotopically labeled chemicals We would derive therefrom precise knowledge of the uptake or "appetite" pattern of that neoplasm From this, one should be able to write a prescription for a "reducing diet" of antimetabolites which would specifically restrain or altogether destroy that particular cancer

A second way of employing human cancer implants is to use them as assay objects for routine screening of candidate compounds for cancer chemotherapy Few tests have been made so far, but such limited data as are available suggest that this is a perfectly practicable procedure, capable of revealing specific susceptibilities of the neoplastic cells

These implants can not only be employed in testing chemicals. They provide ideal culture material for the growth and adaptation of potentially oncolytic viruses. Indeed, their use in this fashion has already yielded virus strains which are destructive of human cancer at an extremely high dilution, and which are much less injurious to the normal human cells subjected to test.

Finally, preliminary studies already suggest that the technique of human cancer culture will permit much more accurate studies of those factors of environment, the milieu, offered by the host to the cancer. For example, the various biologically active steroids, or fractions from the pituitary gland, lend themselves well to exact measurement of their effects on human cancer growth or inhibition The influence of stroma, of humoral immunity, of diet, of essentially every conceivable metabolic factor of the host, can be precisely examined.

Human cancer for test in vitro can be to the cancer problem what the

cultured bacterium has been to the control of infectious disease. Let us hope that actual experience bears out our high hopes for this technique

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Appendix

Atlas of Case Presentations: Pitfalls in Diagnosis and Lessons Learned in Retrospect

EDGAR MAYER, ISRAEL RAPPAPORT, AND HERBERT C. MAIER

INTRODUCTION

It is the customary procedure in most medical textbooks to make use of illustrated case histories for demonstration of the characteristic features of the disease under discussion. Here we are digressing from this procedure and are presenting a series of illustrated case histories with a totally different purpose in mind. Throughout this book we have stressed detection of the incipient and the earliest perceivable manifestations which should raise the suspicion of cancer of the lungs. Repeatedly we have emphasized the fact that it is a grave mistake to look and wait for features characteristic of this disease, that there is nothing characteristic about incipient lung cancer, that in this earliest phase diagnosis must begin with suspicion, and that a high index of suspicion must be developed by long clinical experience. Our experience has taught us that the clinical acumen necessary for ever earlier detection of cases of incipient lung cancer is best acquired by lessons learned in retrospect from mistakes made and pitfalls encountered and remembered. We therefore propose to present illustrated case histories to demonstrate the pitfalls encountered and the errors made as we have found them—and made them ourselves in some cases—as well as the lessons we have learned and applied in other cases.

It should be pointed out that the series of illustrated case histories shown here represents a true picture of everyday experience with lung cancer. It is the purpose of the case presentations to bring home one most important lesson, which is that every patient with incipient lung cancer presents individual problems in diagnostic study and investigation, and that from each of these some lessons can and should be learned. Unfortunately this is still too often not realized until too late in retrospect.

CASE #1

This 40-year-old male complained of pains in his joints, especially the ankles and knees, of nine months' duration X-rays of the extremities on January 29, 1947, had shown marked periosteal thickening (Fig. IA) Originally the patient had been treated for rheumatoid arthritis; later other bone and joint conditions were considered. A routine posteroanterior chest film on March 19, 1947, was considered negative (Fig IB) except for some hilar calcification and emphysema. The typical picture of pulmonary osteo-arthropathy which this patient manifested was not recognized at that time A lateral roentgenogram on March 24, 1947, demonstrated a tumor mass in the lower posteromedial portion of the left lung which had been obscured by the overlying cardiac silhouette on the posteroanterior roentgenogram (Fig. IC) Following lobectomy, the joint tenderness and swelling dramatically disappeared within a few days

LESSONS:

1 The first clinical manifestation of some cases of bronchogenic carcinoma is the presence of swelling and tenderness of certain joints. Rheumatoid arthritis is usually incorrectly diagnosed.

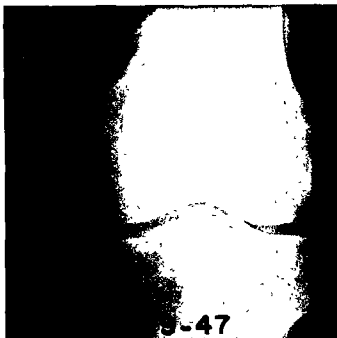
2 When clubbing of the fingers is present with joint manifestation, an intrathoracic lesion should be suspected

3. Many patients with pulmonary osteo-arthropathy due to cancer of the lung have a small peripheral lesion which can be obscured by other structures such as the cardiac silhouette or even an overlying rib.

4 Intensive radiologic investigation of the lung fields, including tomographic studies, is indicated in any patient with clubbing of the fingers and arthralgia, unless some other known cause for this condition is established.

5 Removal of the bronchogenic carcinoma in patients with joint manifestations results in immediate dramatic subsidence of the periarticular tenderness and swelling

Fig 1A



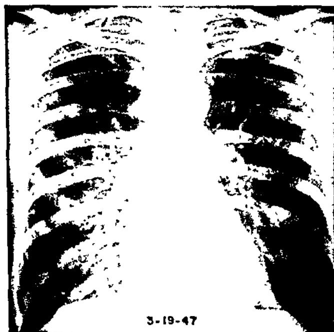




Fig IC

CASE #11

Male, aged 65 years (in 1946), was examined for hoarseness and found to have tuberculous laryngitis accompanying an active tuberculous process in the left apex He was treated in a sanatorium for one year and then considered well and remained so, as shown in follow-up examinations for the next five years (Fig IIA and B). In February 1952 a new small soft nodular lesion was noted on x-ray (Fig. IIC) at the lower border of the previously involved area in the left upper lobe, giving the appearance of a recent extension of the old process. No other signs or symptoms of active tuberculosis had been present, and sputa remained negative Careful study of previous x-rays at that time revealed that the recently discovered nodular lesion had been growing in size but was undiscovered because of its small size so that it had remained hidden under rib shadows on previous x-rays since 1948 The new lesion of three years' duration failed to arouse suspicion of neoplasm even though sputum remained negative for tubercle bacilli, and its tuberculous nature was taken for granted. The patient, now 72 years old, refused to resume treatment for tuberculosis and failed to return for examination for the next two years Next seen in 1954, he again complained of hoarseness, but this time it was due to a recurrent laryngeal paralysis The x-ray (Fig. IID) and physical signs including metastatic nodes in neck clearly indicated an inoperable bronchogenic cancer

Lessons:

1. The incipient phase of bronchogenic cancer is probably the longest in duration, its growth from tiny nodule to visible mass may take two years, and another two years may pass before the tumor begins to encroach on mediastinal structures.

2. The smallest neoplastic nodule which can be visualized by x-ray is considered to be about 3 mm in diameter

3 Such a small nodule will certainly escape discovery particularly when projected with the shadows of other structures, even if previous x-rays are available for comparison

4 Cancer must be suspected and x-rays must be carefully studied with that suspicion in mind, if we are to discover it in the early stage.

5 Bronchogenic cancer associated with a pulmonary tuberculous process often occurs in the same part of the lung, thereby greatly increasing our diagnostic problems

6 In patients of cancer age with arrested tuberculosis, appearance of a new lesion should be looked upon with suspicion Careful search for other signs of active tuberculosis should be made, and the possibility of cancer should be ruled out

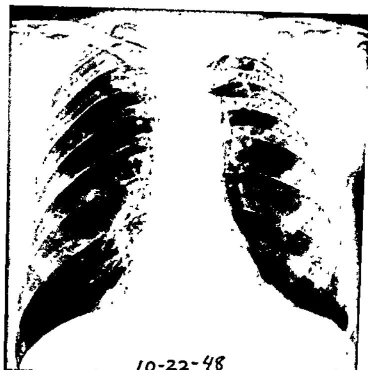


Fig IIA

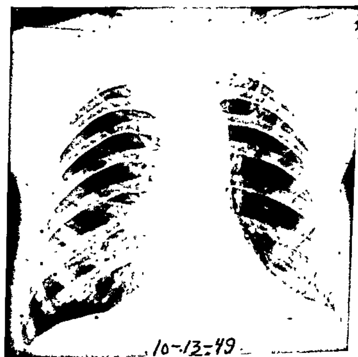


Fig IIB

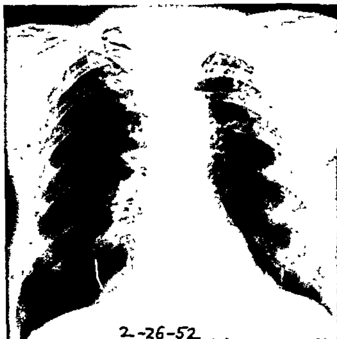


Fig 11C



Fig 11D

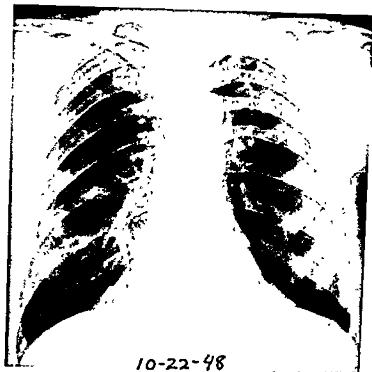


Fig. IIA

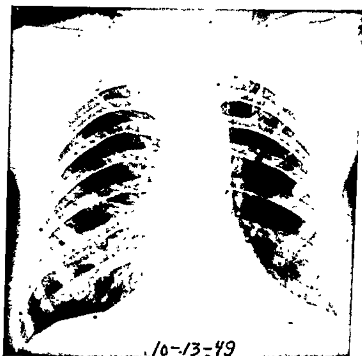
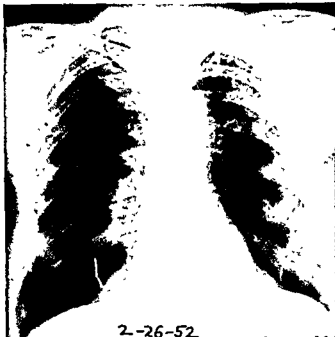


Fig. IIB

Fig IIC



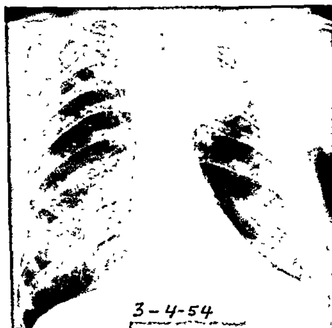


Fig IID

CASE #III

Male, aged 66 years, a fur worker, had been treated for "fur asthma" for 15 years, since 1935. The asthma was greatly aggravated for last five years and had compelled patient to stop work. X-ray in October 1950 revealed nothing significant aside from emphysema (Fig. IIIA).

During the next year patient noted great increase in wheezing, cough, and expectoration. Physical examination then revealed spastic bronchitis and emphysema compatible with diagnosis of long-standing allergic bronchitis However x-ray (Fig IIIB) taken two years later (July 1953) showed a mass in right lung field with a central rarefaction which was incorrectly diagnosed as an infected emphysematous bulla The patient refused operation but remained under treatment for his "asthma" for the next two years When examined two years later the findings conclusively indicated far-advanced neoplastic disease with large firm nodes in the right axilla and right supraclavicular space, and paralysis of the right diaphragm. X-ray (Fig IIIC) at this time (January 1955) revealed a density occupying the upper two-thirds of the right lung with evidence of large cavity

LESSONS.

1. Development of lung cancer was long overlooked because its symptoms blended with and aggravated those of a pre-existing allergic bronchitis and asthma of occupational origin

2. Necrotic cancer with fluid level can simulate infected emphysematous bulla or a pyogenic lung abscess

Fig IIIA





Fig IIIB

CASE #IV *

This 48-year-old male, a heavy smoker, had a pneumonitis in the right lower lobe. Following chemotherapy the symptoms at first disappeared but later cough and fever returned. Although the subsequent postero-anterior roentgenogram of the chest showed little residual abnormality, the lateral film clearly demonstrated residual infiltration at the extreme base (Fig IVA and B). Bronchoscopy revealed a carcinoma in a branch bronchus of the right lower lobe Pneumonectomy was performed without delay.

LESSONS:

1. Need for bronchoscopy in recurrent pneumonitis.
2. Need for lateral x-rays
3. Necessity for serial roentgenograms to demonstrate complete clearing of the inflammatory process before ruling out carcinoma

* Courtesy of Dr John LaDue, Memorial Hospital, New York City

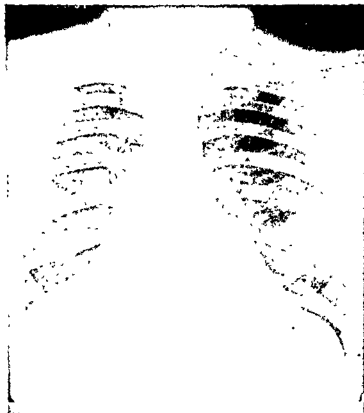


Fig IVA



Fig IVB

CASE #V

Male, aged 61 years, nonsmoker, had had periodic examinations twice yearly for five years, including chest x-rays once yearly. He was a squat individual with a broad, deep, and short chest with prominent veins over the anterior upper chest extending towards shoulders. In December 1953 when the last normal x-ray was obtained (Fig VA), he complained of a vague sensation of pressure in the right upper chest This had been noted periodically for one and a half to two years, especially in association with upper respiratory infection and cough Recently he began to experience fever-like flushes associated with aching joints and muscles. These attacks would last a few hours, caused sweats, and were followed by prostration. Susceptibility to "colds" developed, and during the winter months of 1953-1954 acute respiratory infections were particularly frequent and accompanied by persistent unproductive coughing. In June 1954 examination indicated only mild tracheobronchial catarrh and fluoroscopy of chest revealed no apparent change During the next month the cough became hard, increasingly more spasmodic and brassy in character When next seen in August 1954, x-ray (Fig VB) revealed a mass in the right upper lobe Bronchoscopy was negative At operation a week later, an egg-sized tumor mass was removed with the right upper lobe and proved to be squamous cell carcinoma The superior vena cava was also found to be involved Postoperative supervoltage radiotherapy was instituted with temporary improvement (Fig VC)

LESSONS

1. Symptoms suggestive of mediastinal involvement preceded the actual x-ray evidence of lung tumor by one or two years.

2. Rheumatoid symptoms preceded demonstrable growth by at least one year.

3 Persistent cough preceded demonstrable growth by at least six months

4 Male nonsmokers occasionally develop squamous cell bronchogenic cancer

5. More frequent follow-ups with x-ray studies might have led to earlier diagnosis

12.15.53.

Fig VA

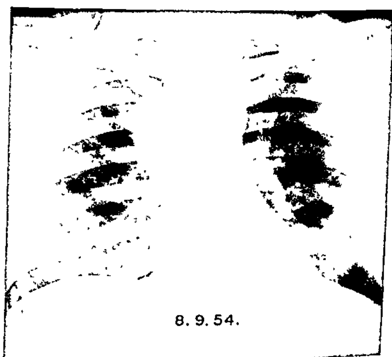


Fig VB

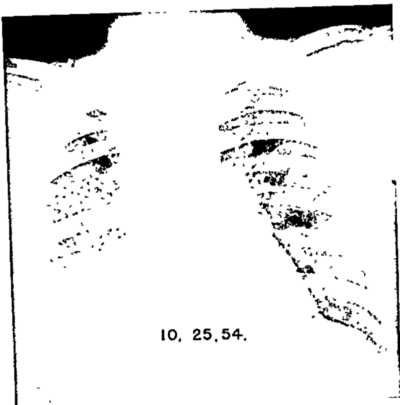


Fig VC

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Fig VA

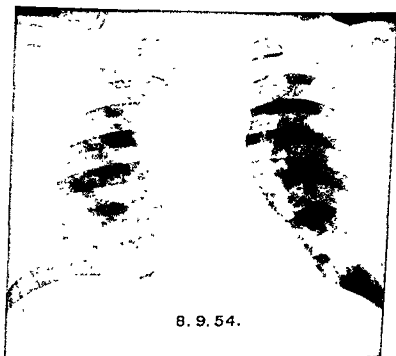
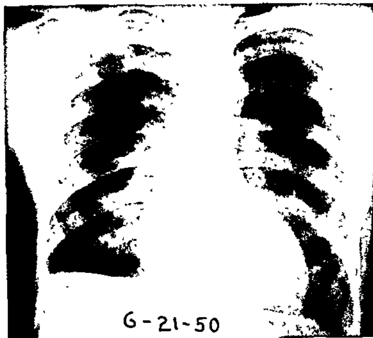


Fig VB

Fig VIA



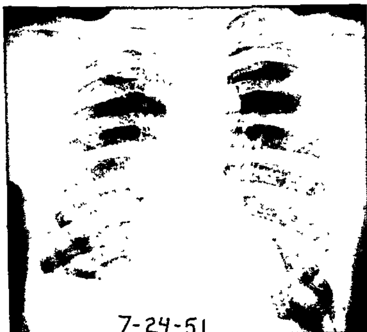


Fig VIB

CASE #VI

Male, aged 51 years, on routine x-ray survey in June 1950, had a small peripheral density in the third right interspace (Fig. VIA). Because of presence of old pleural thickening extending from the pleurodiaphragmatic angle upward into the right chest, the density was considered to be merely thickened pleura. Suspicion of neoplasm was aroused when five months later patient complained of vague sensations of tightness across right chest The lesion was watched for another eight months and although it did not appear to have changed, the symptoms persisted and exploratory thoracotomy was performed in August 1951 (Fig VIB). A solitary nodule measuring approximately 2.5 cm was resected with a wedge of the right middle lobe. This proved to be adenocarcinoma The patient was reported well in June 1953.

LESSONS

1 Peripheral coin lesion was observed for 11 months, with the wrong belief that it represented thickening of pleura.

2 Mild persistent thoracic complaints otherwise unexplained and occurring at the cancer age should at least bring to mind the possibility of lung cancer, and in this patient led to exploratory thoracotomy while the lesion was fortunately still operable.

Fig VIIA





Fig VIIB

CASE #VII *

Male, aged 37 years, in 1952 had far-advanced pulmonary tuberculosis involving both upper lobes with large cavity on left (Fig. VIIA). Chemotherapy given for nine months, then thoracoplasty on left side in 1953. In April 1953 sputum reported Gaffky II, the residual lesion in second right interspace was the suspected source (Fig. VIIB). In November 1953 this lesion was removed by wedge resection (Fig. VIIC).

Pathologic report: epidermoid carcinoma arising in wall of tuberculous cavity. Growth restricted to wedge resected. Patient well since then, last seen July 1955.

LESSONS

1. A case of lung cancer resected in the truly incipient phase, discovered by accident and arising in wall of a tuberculous cavity.

2. Unusual persistence of x-ray shadows and other signs despite prolonged therapy in tuberculous, more particularly in the aged, should at least suggest a possibility of coexistent neoplasm.

3. The surprising feature here was the young age of the patient.

4. Coexistence of carcinoma and tuberculous is not considered unusual.

* Courtesy of Dr. G. E. Wilson of the Will Rogers Hospital, Saranac Lake, N. Y.

Fig VIIA

5. 2. 52

4. 6. 53.

Fig VIIB

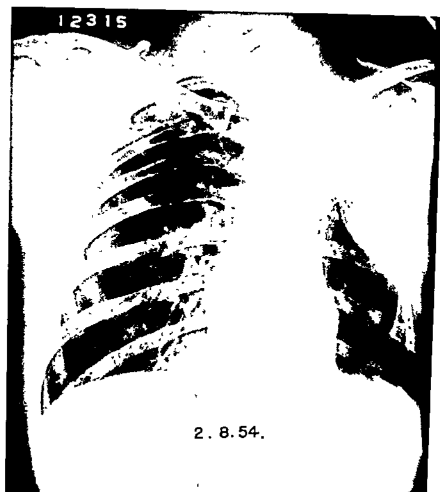


Fig VIIC

CASE #VIII*

A 50-year-old male, heavy smoker, had a complete examination in a cancer detection clinic in November 1949. The following month he developed a respiratory infection with wheezing. Symptoms responded to antibiotics but x-ray (Fig VIIIA) showed an increased left hilar shadow. Bronchoscopy revealed a carcinoma in the left lower lobe bronchus. Pneumonectomy performed February 1950. Patient well on last follow-up visit.

LESSONS

1. Need for complete re-evaluation of any case presenting new symptoms even though a chest x-ray a short time previously was considered normal.

2. Early bronchoscopy may establish a diagnosis in some cases of bronchogenic carcinoma at a time when the interpretation of the roentgenogram may be equivocal.

3. Localized wheezing demands bronchoscopic examination.

* Courtesy of Dr John LaDue

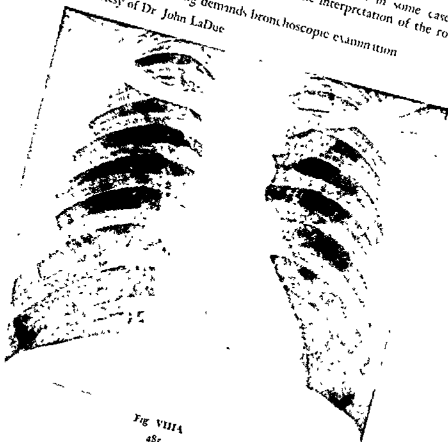


Fig VIIIA

CASE #IX

Male laborer, aged 38 years, complained of chest pain following trivial injury. X-ray was negative for suspected rib fracture but marked enlargement of right hilar area and widened upper mediastinum were found (Fig IXA) This did not immediately raise suspicion of malignancy, probably because of young age of patient and his prompt recovery. He returned to laborious work until hemoptysis occurred two months later, again following trivial chest trauma to which bleeding was attributed Even then patient denied symptoms except for occasional pain in chest and mild cough with expectoration X-ray then showed massive involvement of right lung and pleura (Fig IXB). On exploration large unresectable carcinoma was found extending from right middle lobe. Biopsy disclosed undifferentiated cell cancer. Supervoltage radiotherapy resulted in much shrinkage of tumor and apparent prolongation of life for eleven months.

Lessons

1. Progression of cancer to an extent involving a whole lung may be so insidious as to be compatible even with hard manual labor.

2 Accidental trauma by eliciting pain or hemoptysis may afford the first opportunity to reveal a growing tumor at an early stage.

3 A suspicion of lung cancer should not be discarded because of an apparent explanation for the chest pain (in this case, trauma) when an x-ray shadow persists

Fig IXA

9. 7. 54.

11. 24. 54.

Fig IXB

CASE #X

Male, aged 51 years, first seen May 1950, gave history of smoker's cough for many years. In 1947 patient had hurt chest in a fall and x-ray taken to delineate ribs showed no bony change. However, a large walnut-sized shadow at left base was noted and misinterpreted as traumatic pleurisy (Fig. XA) In January 1950 the smoker's cough changed its character and became more spasmodic. This was ignored. Bloody sputum developed in March 1950 X-ray and physical examination in May 1950 revealed homogeneous density in left lower lobe with pleural involvement and small amount of fluid (Fig. XB). Thoracotomy in May 1950 revealed presence of a tumor in lower part of left lower lobe with numerous firm hilar and mediastinal lymph nodes, and seeding of parietal pleura, left hemidiaphragm, and pericardium. Resection was decided against. Biopsies all revealed squamous cell carcinoma The patient had a post-operative death in March 1951 following resection by another surgeon at urgent request of family.

LESSONS

1 Long duration This tumor was already of large walnut-size in 1947. Considering that in slowly growing tumors the early phases are probably of longest duration, this neoplasm had as long a period of growth before clinical symptoms occurred as it had in the succeeding period The total duration of growth may therefore have exceeded five years

2. Completely asymptomatic growth of peripheral neoplasm lasted for over three years.

3 Misinterpretation of original x-ray shadow was that of traumatic pleural change

4 No attention was paid to the definite change in nature of the smoker's cough.

Fig. XA

Oct. 1, 1947

Fig. XB

5-4-50

CASE #XI *

Male, aged 49 years, in March 1945 had cough with moderate expectoration and recent hemoptysis Sputum positive for tubercle bacilli, x-rays showed evidence of moderately advanced tuberculous lesions in both upper lobes with large cavity in left apex. Left pneumothorax begun in April 1945, continued for three years. Sputum turned negative. Routine check in February 1949 showed marked increase of lesions in central part of right upper lobe with new circumscribed x-ray density suspicious of tumor (Fig. XIC). Sputum persistently negative except for one specimen (Gaffky I). Bronchoscopy negative and aspirated material negative for tumor cells. Planigrams showed definite tumor mass Functional tests indicated grave risk of pulmonary failure. Death a few months later—no autopsy

LESSONS

1. X-ray of 1946 and 1947 (Fig XIA and B) suggest beginning increase of hilar density where two years later large tumor was discovered Preexisting tuberculous process camouflaged clinical and x-ray signs which should have led to suspicion of growing tumor much earlier.

2 New hilar mass developed at root of less involved lung while more affected lung was under pneumothorax therapy.

3. New lesion developed and enlarged while sputum became negative.

4 In 1946 new hilar mass whose outer border extended more than 8 cm from mid-line was noted during left-sided pneumothorax treatment. This had further increased by 1947 and attained large size in 1949 while the tuberculosis was improving

* Courtesy of Dr. G. E Wilson of the Will Rogers Hospital, Saranac Lake, N Y

Fig XIA

10.21.46.

8.11.47.

Fig XIB

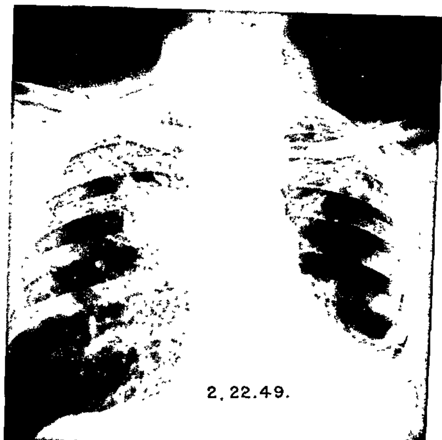


Fig XIC

CASE #XII

A 33-year-old woman with symptoms and roentgen findings of pyloric obstruction was thought to have a carcinoma of the stomach The mass *in the right lower lobe which is partly obscured by the dome of the diaphragm* was considered to be probably a pulmonary metastasis (Fig XIIA) Thoracotomy revealed a peripheral bronchial adenoma which was resected Subsequent abdominal exploration demonstrated a benign gastric ulcer for which a partial gastrectomy was performed Patient well

LESSONS

1. Value of exploratory thoracotomy in doubtful cases
2. A solitary pulmonary mass may or may not be related to a suspected or proven neoplasm elsewhere

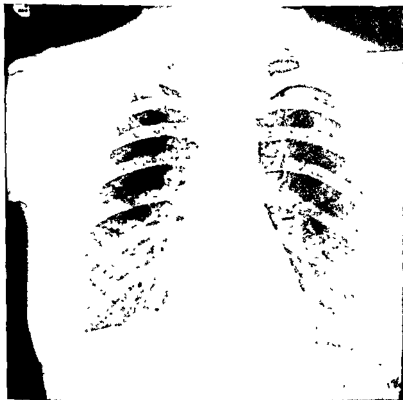


Fig. XIIA

CASE #XIII

Male, aged 69, first seen in May 1943 for a hard productive coug worse in the recumbent position. This cough, previously mild wit occasional expectoration, had been present since attack of coronar thrombosis with mild congestive failure sustained in 1942. In the first x-ray (Fig XIIIA) the left hilar shadow appeared somewhat enlarged, but in light of history and physical signs was interpreted as due to chronic pulmonary congestion In the next three years the patient had recurrent attacks of chest pain thought to represent angina pectoris due to coronary sclerosis In September 1946 hemoptysis occurred which led to restudy of lungs The chest x-ray then showed (Fig XIIIB) a density at the left hilum obviously indicating neoplasm Age and cardiac status precluded surgery. In another six months growth led to bronchial obstruction and involvement of the left lower lobe (Fig. XIIIC).

LESSONS

1. Diseases of advanced age (cardiovascular) with pulmonary complications are common accompaniments in the age period in which bronchogenic cancer occurs.
2. Chest pain and chronic pulmonary congestion were thought to be due entirely to coronary disease with heart failure and so possibility of bronchogenic cancer was not even considered.
3 The incipient phase lasted here over three years.
4 The initial symptom was a changed character of the cough.
5 Unilateral increase of the hilar shadow is characteristic of neoplastic disease but can be misinterpreted as congestive failure in presence of other evidence indicating pulmonary congestion

Fig XIIIA

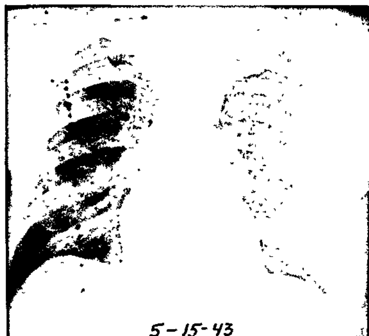




Fig XIIIB

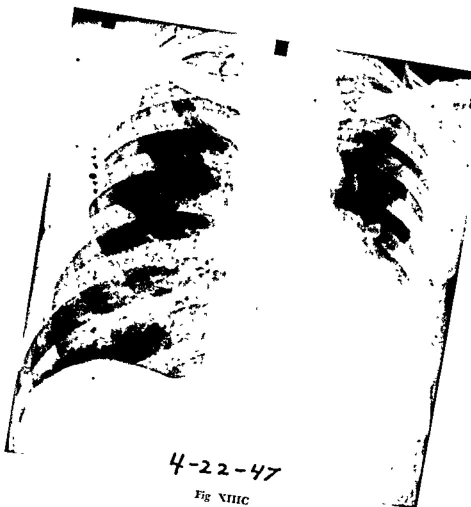


Fig XIIIC

CASE #XIV

This 58-year-old male was receiving chemotherapy for proven tuberculosis with cavity in the hilar region of the left lung. X-ray in January 1954 showed no obvious lesion in the right lung. Six months later a rounded density was noted in the right upper lobe close to the hilum (Fig XIVA). Since this patient was receiving adequate chemotherapy for tuberculosis at the time the lesion in the right lung developed, it was considered rightly that this was not a tuberculous lesion. The lesion in the left lung had greatly improved by this time. A right thoracotomy was done without delay. A squamous cell carcinoma of the right upper lobe was found and lobectomy performed. Patient well and working without dyspnea one year later.

LESSONS

1. Carcinoma of the lung should be suspected when atypical lesions appear in a patient under treatment for tuberculosis.
2. Surgical excision of a cancer in one lung may be feasible even though the opposite lung is the site of another disease.
3. By performing lobectomy rather than pneumonectomy in selective cases, rehabilitation may be facilitated.

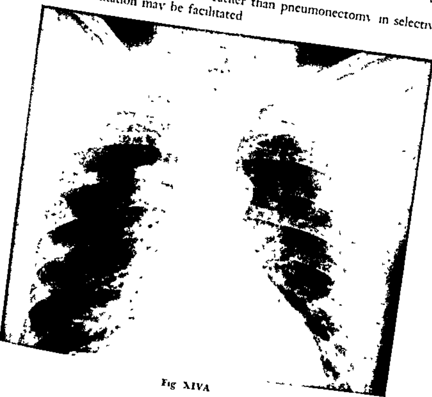


Fig XIVA

CASE #XV

Male, aged 64 years, a heavy smoker, had "smoker's bronchitis" years, increasingly troublesome in recent years. Examination in 19 revealed signs of chronic bronchitis, emphysema, much cough, expecto tion, and shortness of breath. X-ray revealed fibrotic residues in upp lobes from tuberculosis in youth. Symptoms increased recently wit recurrent attacks of acute bronchitis and so treated periodically for nev few years In July 1946 there was increased and persistent wheezing, with cough, expectoration, and dyspnea unchanged. Examination then revealed cachexia and loss of weight. Physical and x-ray evidence of obstructive emphysema localized to the left upper lobe (Fig. XVA) was then noted but was looked upon as part of a chronic but progressive emphysema. He was not seen again until end of 1947 when complaints of mental confusion and speech difficulties led to careful neurologic study, resulting in a diagnosis of brain tumor. Clinical and x-ray signs in the chest then revealed evidence of bronchogenic cancer (Fig. XVB) and left little doubt as to metastatic origin of brain tumor.

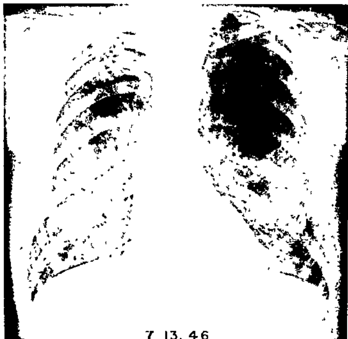
LESSONS

1 Obstructive emphysema involving the left upper lobe was the first clinical evidence of bronchogenic cancer

2 Initial development of the lung cancer was obscured by preceding chronic bronchitis and emphysema.

3 Brain metastasis first led to its clinical recognition but it should have been suspected at least one year previously from the change in pulmonary symptoms and signs

Fig XVA



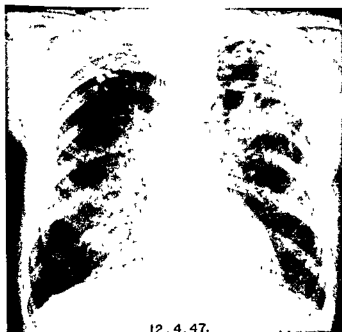


Fig XVB

CASE #XVI

This 63-year-old male was a heavy smoker and had been slightly dyspneic for five years with hypertension and cardiac hypertrophy. Pinkish sputum was first noted after some teeth were extracted, and was at first considered related to this. Bronchoscopy was negative. The large heart obscured the left lower lung field (Fig. XVIA). After three weeks of chemotherapy, a small hemoptysis again occurred. Operation was then recommended with the hope of performing a lobectomy. At operation, however, the extent of the tumor made pneumonectomy mandatory for complete removal of the lesion. Pathologic examination revealed an adenocarcinoma with lymph node metastasis. Postoperatively the patient required prolonged oxygen therapy and close supervision because of very limited respiratory reserve. Six months later the patient was handicapped by dyspnea on exertion.

LESSONS

1. Carcinoma of the lung may be difficult to differentiate from pulmonary congestion in patients with heart disease.
2. A large cardiac silhouette can obscure a lesion of considerable size in the left lower lobe.
3. In patients with limited cardiorespiratory reserve, the difference between pneumonectomy and lobectomy may greatly affect the patient's subsequent course.
4. Pneumonectomy in patients bordering on pulmonary insufficiency requires individualized oxygen therapy program in the postoperative period.
5. Hemoptysis may erroneously be assumed to be blood from the gums, throat, or nose and thus not given its true significance.

CASE #XVII *

Male, aged 58 years, in February 1945 suffered traumatic cerebral concussion; since then disabled because of headache and dizziness. One year later began to lose weight and raise blood-streaked sputum Tuberculosis was diagnosed. In October 1946 clinical and x-ray findings showed extensive process involving entire left lung with shift of mediastinum (Fig. XVIIA) Sputum Gaffky IV, E.S.R. 125 mm, weight loss 25 lbs Bronchoscopy showed granulations 4 cm below carina in left main bronchus but biopsy revealed squamous cell carcinoma. Pneumonectomy in January 1947 in spite of involvement close to carina Pathologic examination indicated presence of large tuberculous cavity in left upper lobe, and squamous cell carcinoma in left main bronchus Patient remained well for next 18 months (Fig. XVIIB), when metastases appeared with death in July 1949

LESSON

1. Tuberculosis is here associated with bronchogenic cancer and apparently developed simultaneously. The same clinical picture may be produced by either Presence of positive sputum is usually considered sufficient to diagnose tuberculosis and by implication to exclude cancer, but this is not always true. In approximately 10 per cent of cancer cases, associated tuberculosis is found. Atypical features of clinical picture should lead to suspicion of either tuberculosis complicating cancer or the latter complicating tuberculosis.

* Courtesy of Dr G E. Wilson of the Will Rogers Hospital, Saranac Lake, N Y.

Fig
XVIIA

10. 26.46.

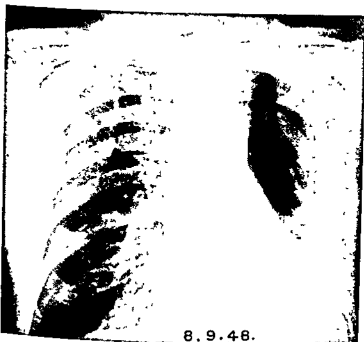


Fig
XVIIB

CASE #XVIII *

Housewife, aged 41 years, at Memorial Center for Cancer and Allied Diseases in 1938 treated for cystic mastitis. Uneventful course until September 1947 when she gave history of cough and hoarseness for two months. X-rays showed coin lesion at right second rib interspace (Fig XVIIIA). Bronchoscoped October 23, 1947, with no abnormal findings Bronchial washings Pap II. Five negative Pap sputums during 1947–1948 Five negative studies for tuberculosis All other laboratory studies were negative Slight enlargement of the coin lesion over next two years (Fig XVIIIB) led to right pneumonectomy September 1, 1949, with microscopic diagnosis of alveolar carcinoma Had uneventful recovery and was last seen on September 20, 1954, with no evidence of recurrent disease

LESSONS

1. Repeated negative laboratory studies including microscopic study of sputa and bronchial washings will not exclude diagnosis of carcinoma

2 Delay of two years before pneumonectomy was not justified, patient's resistance to operation was the cause.

3. Most peripheral coin lesions give negative bronchoscopy and negative cytology findings.

* Courtesy of Dr John LaDue.

CASE #XIX

A male, aged 52, was diagnosed as having a so-called pneumonitis a had an ill-defined right hilar x-ray shadow in September 1951 (Fig. XIXA with complaints of nonproductive cough and hemoptysis He was see again in June 1952 with same symptoms and x-ray showing clearing but a persisting enlarged right hilum (Fig. XIXB). Patient was admitted for bronchoscopy after cytologic study of sputum was positive for cancer (Grade V). Biopsy of a granular tumor at the entrance of the middle lobe bronchus revealed epidermoid carcinoma. Biopsy of the carina showed normal mucosa A right radical pneumonectomy was immediately carried out, and the postoperative convalescence was without incident. The pathologic report was that of bronchogenic carcinoma in the right main stem bronchus beginning 4 cm. below the line of bronchial transection with metastasis to adjacent but not to the highest or lowest lymph nodes removed from the mediastinum. The patient is well, without evidence of recurrent disease on January 9, 1955.

LESSONS.

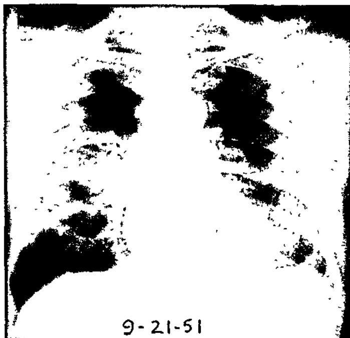
1 Pneumonitis associated with nonproductive cough and hemoptysis was here the early evidence of bronchogenic cancer.

2. Clearing of the pneumonitis left an ill-defined enlargement of the right hilar shadow which should have suggested neoplasm earlier.

3. Recurrence of hemoptysis with pneumonitis eight months later led to bronchoscopy and cytologic studies

4. The tumor was found resectable in spite of eight months' delay in diagnosis.

Fig XIXA



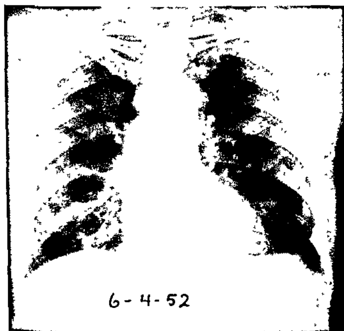


Fig XIXB

CASE #XX

A 61-year-old male with the symptoms of a respiratory infection in September 1945. Change in character of cough noted First x-rays showed several areas of density in the left lung with subsequent clearing of all except one lesion (Fig. XXA). Therefore, carcinoma was suspected Exploratory thoracotomy revealed a squamous carcinoma of the bronchus Pneumonectomy performed. Patient free of evidence of recurrence six years later but has had some shortness of breath since operation.

Lessons·

1. When several separate areas of infiltration are present on the roentgenograms, all may not be of the same etiology. Some may be on an inflammatory basis while one area of density may represent a carcinoma

2. Serial roentgenograms at short intervals after a pulmonary infection are indicated

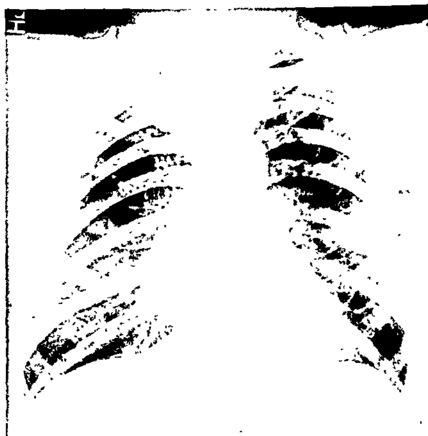


Fig XXA

CASE #XXI *

Male, aged 62 years, heavy smoker, had pneumonia in March 1953. Since then loss of much weight, increasing dyspnea, some cough with little expectoration. In November 1953 bilateral pleural effusion considered due to "heart and kidney trouble." Early 1954 persistence of chest findings led to studies with bronchoscopy and cytologic search for tumor cells in bronchial washings, pleural fluid, and sputum. All were negative. In March 1955 restudy showed large tumor in right and a pneumonitic process in left lower lung (Fig XXIA). Bronchoscopy then revealed occlusion of right middle lobe bronchus and infection in other bronchi. Cytology suggested neoplasm. Exploration proved to be very successful. Large tumor was found in right middle lobe with direct involvement of parietal pleura in front. Right lung was resected together with frontal parietal pleura. Postoperative course was stormy but patient left hospital after three weeks in good condition (Fig XXIB). Tumor was epidermoid carcinoma. The patient last seen four months after operation showed gradually increasing pulmonary capacity.

LESSON:

The tumor proved to be resectable in spite of history indicative of growth of about two years' duration, in spite of extensive pleural involvement, and in spite of extensive inflammatory (suppurative) process in the other lung. Resectability is often quite unpredictable from clinical and x-ray evidence.

* Courtesy of Dr. E E Rockey of New York City

3. 16. 55.

Fig XXIA



Fig XXIB

CASE #XXII

Male, age 46, heavy smoker. In January 1953 routine periodic chest x-ray (Fig. XXIIA) was normal except for hilar calcifications. In August 1954 x-ray shows discrete infiltration in second right interspace (Fig XXIIB). Only symptom was long-standing cough with mucoid sputum, attributed to smoking These symptoms abated promptly upon cessation of smoking. Because of patient's delay, next x-ray six months later, February 1955 (Fig. XXIIC), indicated slight increase of infiltration Planigrams three months later (Fig XXIID) revealed two isolated spherical nodules located posteriorly in lung periphery Clinical studies then revealed following: Tuberculin skin test markedly positive. Histoplasmin skin test negative, complement fixation negative Bronchoscopy negative Bronchial washings and sputa negative for bacilli, fungi, cancer cells Cultures negative for tubercle bacilli Exploration revealed neoplasm which proved on resection to be bronchiolar carcinoma (localized)

LESSONS

1. Early bronchiolar carcinoma simulated early tuberculosis in location as well as in form

2 Planigrams revealed dense and sharply defined nodules where conventional films showed discrete infiltrations with hazy borders

3 Earlier planigraphic and clinical studies might have led to earlier exploration and resection

4 Loss of cough and expectoration upon cessation of smoking is of no significance when x-ray shadow persists, and should not lull suspicion of malignancy.

1. 13. 53.

Fig XXIIA

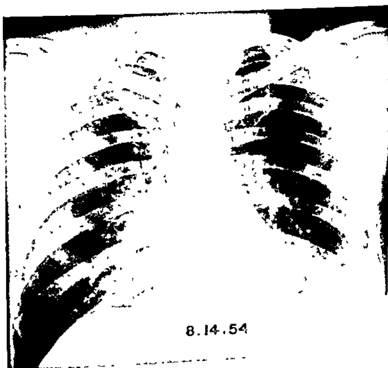


Fig XXIIB

2.21.55.

Fig XXIIC

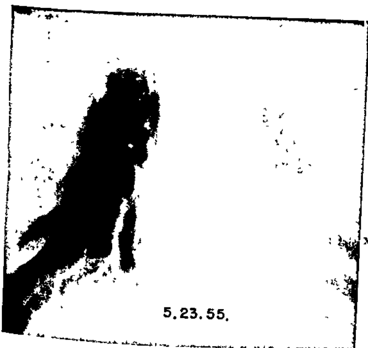


Fig. XXIID

CASE #XXIII

43-year-old woman whose only complaint was progressively increasing dyspnea which began very insidiously about three to four months previous to the date of the x-ray shown here (Fig XXIIIA). Cough with scant mucoid expectoration appeared during the past few weeks. There were no other constitutional symptoms at any time. Careful history and thorough clinical study tended to exclude any diffuse infectious pulmonary process including granulomatosis and mycosis. Because of unusually strongly positive tuberculin reaction the possibility of tuberculosis was entertained for a short period of time. Although no scalene node was palpable a scalene biopsy was successful in securing tissue which proved to be characteristic of pulmonary adenomatosis. The patient died of progressive cardiopulmonary failure about one year later. Diagnosis was verified.

LESSONS.

1. We believe the pulmonary adenomatosis began here in form of a solitary round lesion in right upper lobe and soon led to bilaterally disseminated carcinomatosis.

2. Scalene biopsy even in absence of a palpable node can often prove to be of particular diagnostic value.

3. A strongly positive tuberculin test in diffuse pulmonary disease may at times be very misleading.

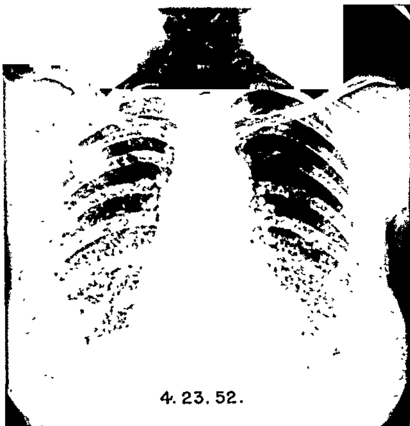


Fig XXIIIA

CASE #XXIV

A 71-year-old man was under observation and treatment in 1955 for advanced arteriosclerotic cardiovascular disease, vascular hypertension, and advanced diabetes Intermittent claudication had existed for ten years A coronary thrombosis had occurred in 1947. In October 1955 chest x-ray (Fig. XXIVA) revealed a spherical shadow near root of right lung without pulmonary symptoms, but because of unsatisfactory cardiac status, bronchoscopy was not resorted to Patient remained free of pulmonary complaints. One month later chest x-ray (Fig. XXIVB) showed unchanged lesion on anterior-posterior view but additional area of atelectasis extending into anterior part of right upper lobe on lateral view (Fig. XXIVC). Then patient suddenly developed symptoms of coronary occlusion in addition to expectorating blood-stained mucoid sputum. Two specimens showed squamous cell carcinoma by cytologic study (Dr. Papanicolaou). Within next few days patient suffered acute attacks of recurrent precordial pain. Electrocardiogram showed progressive changes indicative of antero-lateral septal myocardial infarction For next six weeks on bed rest and slow return to ambulation, cardiac recovery was excellent. X-ray remained unchanged and patient was then explored surgically three months after discovery of neoplastic lesion in right upper lobe. One walnut-sized and two smaller pea-sized nodules were found in central part of successfully resected right upper lobe. Regional lymph nodes were free of neoplastic tissue. Pathological findings revealed squamous cell carcinoma in right upper lobe with atelectasis of anterior segment. Regional and mediastinal lymph nodes were uninvolved.

LESSONS:

1 Close observation of patient for unrelated conditions caused discovery of bronchogenic cancer in fairly early phase, although age of patient and cardiac status militated against more aggressive diagnostic procedures

2 Acute coronary occlusion delayed exploration for 3 months but did not prevent successful resection of neoplasm by lobectomy.

3. Advanced age and serious complications which coexist (cardiovascular disease, diabetes, etc.) do not preclude radical treatment of bronchogenic cancer, provided this is detected early enough and if status of patient has not deteriorated too much.

Fig XXIVA

10-10-55

Fig XXIVB

11-18-55

This 67-year-old man had clinical and roentgen evidence of pneumonitis in the right middle lobe. The first of several sputum examinations was reported as positive for carcinoma cells but further examinations, including bronchoscopic washings, failed to confirm the presence of cancer. Following antibiotic therapy the pulmonary infiltrate almost completely disappeared on the [illegible] film (Fig. XXVA) [illegible]

was performed and revealed a tiny area of thickening in the medial segmental bronchus of the middle lobe. Middle lobe lobectomy was performed. Frozen section revealed a small carcinoma. It was decided to do no additional resection of lung tissue in this poor-risk patient since the tumor was a fair distance from the line of bronchial transection. The patient's reduced pulmonary reserve was not significantly disturbed by the limited operation performed and the chest x-ray three weeks postoperatively showed excellent pulmonary expansion (Fig. XXVC).

LESSONS:

1. A carcinoma in the middle lobe may simulate the "middle lobe syndrome." Cytologic studies are of particular importance in such cases.

2. Failure to re-confirm a single positive cytologic report must not be given undue weight.

3. A limited resection that apparently completely removes the cancer, although not the ideal cancer operation may be the best compromise in selected cases.

4. Lateral films will often demonstrate a middle lobe atelectasis not demonstrable on posteroanterior films.

Fig XXVA



Fig XXVB

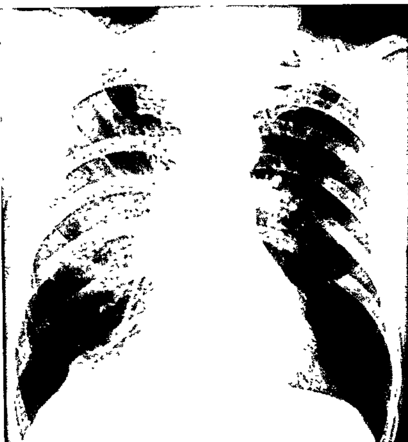


Fig XXVC

Index